UNITED NATIONS ENVIRONMENT PROGRAMME

 INTERNATIONAL LABOUR ORGANISATION

 WORLD HEALTH ORGANIZATION

 INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

 **ENVIRONMENTAL HEALTH CRITERIA 199**

 **Cholordimeform**

 This report contains the collective views of an international group of

 experts and does not necessarily represent the decisions or the stated

 policy of the United Nations Environment Programme, the International

 Labour Organisation, or the World Health Organization.

 Environmental Health Criteria 199

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 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.

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 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. + 41 22 -

 9799111, fax no. + 41 22 - 7973460, E-mail irptc@unep.ch).

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 Environmental Health Criteria

 PREAMBLE

 **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 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 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.

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 IPCS TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR CHLORDIMEFORM

 The Core Assessment Group (CAG) of the Joint Meeting on

 Pesticides (JMP) met at the Institute for Environment and Health,

 Leicester, United Kingdom, from 3 to 8 March 1997. Dr L.L. Smith

 welcomed the participants on behalf of the Institute, and

 Dr R. Plestina 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 chlordimeform.

 The first draft of the monograph was prepared by Dr P. Abbott,

 Canberra, Australia. 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.

 Dr R. Plestina 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

 ACTH adrenocorticotropic hormone

 ADI acceptable daily intake

 a.i. active ingredient

 BSP bromosulfophthalein

 CIMS chemical ionization mass spectrometry

 CNS central nervous system

 CORT corticosteroid

 DNA deoxyribonucleic acid

 EC emulsifiable concentrate

 ECG electrocardiography

 GC gas chromatography

 HPLC high performance liquid chromatography

 IgM immunoglobulin M

 JMPR Joint FAO/WHO Meeting on Pesticide Residues

 MRL maximum residue limit

 Mu Chinese measure of an area equivalent to 1/15 acre

 or 1/60 ha or 166 m2

 MS mass spectroscopy

 NADPH reduced nicotinamide adenine dinucleotide

 NC cell activity natural cytotoxic cell activity

 NK cell activity natural killer cell activity

 NOEL no-observable-effect level

 PL prolactin

 SAP serum alkaline phosphatase

 SGOT serum glutamate-oxalate transaminase

 SGPT serum glutamate-pyruvate transaminase

 SIR standard incidence rate

 SMR standardized mortality ratio

 SPF specific pathogen free

 TLC thin layer chromatography

 TLm median tolerance limit

 UV ultraviolet

 1. SUMMARY

 1.1 Identity, physical and chemical properties, and analytical

 methods

 Chlordimeform is a base of medium strength and forms stable salts

 with strong acids. Both chlordimeform and its hydrochloride salt in

 the pure state are colourless crystalline solids. Chlordimeform base

 has a melting point of 32°C, while the hydrochloride salt has a

 melting point of 225-227°C. Chlordimeform base is sparingly soluble in

 water (250 mg/litre) and readily soluble in organic solvents, whereas

 the hydrochloride salt is readily soluble in water but less soluble in

 organic solvents. Chlordimeform base has a vapour pressure at 20°C of

 48 mPa and a log Kow of 2.89. A wide range of analytical methods are

 available for detection and quantification of chlordimeform in plants,

 soil, water and urine.

 1.2 Sources of human and environmental exposure

 Chlordimeform does not occur naturally. It is manufactured

 commercially by condensation of the Vilsmeier reagent (obtained by

 reaction of dimethylformamide with POCl3, SOCl2 or COCl2) either

 with 4-chloro- o-toluidine or with o-toluidine and subsequent

 chlorination of the resulting intermediate . It has been used as a

 broad spectrum acaricide and is active mainly against motile forms of

 mites and ticks and against eggs and early instars of some

 Lepidoptera insects. It is active in the vapour phase as well as by

 contact. In the early period of its use, it was used on a wide variety

 of crops such as pome fruits, stone fruits, cole crops, vegetables,

 grapes, hops, citrus fruits, apples, pears, cherries and strawberries.

 It was also used in cattle dips for the control of cattle ticks. In

 the latter years, its use was generally restricted to cotton, although

 in some countries, there was continued use on rice. Its registration

 was voluntarily withdrawn in 1988/1989 in most countries. In China,

 production stopped in 1992 and sales ceased in 1993.

 1.3 Environmental transport, distribution and transformation

 Chlordimeform has a moderate vapour pressure but its evaporation

 from plant surfaces is less than would be expected. The hydrolytic

 stability of chlordimeform is strongly pH-dependent; it is stable in

 acid conditions but rapidly hydrolysed in alkaline conditions.

 Chlordimeform has the potential to adsorb to dissolved organic matter.

 In soils, chlordimeform is primarily dissipated by microbial

 action with some contribution by chemical hydrolysis. There is little

 evidence of leaching despite its water solubility, which may be

 due to its adsorption to clay minerals, soil organic matter and

 biodegradation. The principal metabolites are N-formyl-4-chloro-

 o-toluidine and 4-chloro- o-toluidine.

 There is a low but measurable uptake of chlordimeform into plants

 from soil, sufficient to affect plant-feeding pests. When applied to

 the leaves, chlordimeform has only limited capacity to penetrate the

 cuticular layers. Chlordimeform is degraded rapidly in plants. The

 principal metabolites are demethylchlordimeform, N-formyl-4-

 chloro- o-toluidine and 4-chloro- o-toluidine, though not all plants

 studied produced the 4-chloro- o-toluidine.

 In soils, chlordimeform and its metabolites are dissipated

 according to first-order kinetics with a half-life of 20-40 days.

 Bioaccumulation studies have demonstrated low uptake of

 chlordimeform by aquatic organisms and rapid depuration on transfer to

 clean water.

 1.4 Environmental levels and human exposure

 Levels have not been measured in air and water. Following

 applications to paddy fields residues of up to 2900 µg/kg in the top

 5 cm of soil and 150 µg/kg in the next 5 cm have been found.

 Maximum residue levels were set for a wide range of raw produce

 and, in some cases, the residues carried over into processed food. The

 Codex maximum residue limits for chlordimeform have been withdrawn.

 Occupational exposure to chlordimeform has taken place during

 manufacture, formulation and application. In recent years, total

 urinary levels of chlordimeform and its metabolites have been used as

 a monitor for exposure, and the urine level correlates well with the

 degree of skin contamination. Where agricultural workers in the cotton

 industry have undergone extensively surveillance for urinary excretion

 of chlordimeform, the highest exposure levels were in loaders, washers

 and mechanics, with lower levels in flagmen and pilots.

 1.5 Kinetics and metabolism in laboratory animals and humans

 Chlordimeform is readily absorbed from the gastrointestinal tract

 and through the skin of mammals. Rapid excretion follows, with

 approximately 80% in the urine and 10-15% in faeces. Low residue

 levels are evident in all tissues after approximately 10 days, and

 there is no evidence of bioaccumulation. Following dermal

 administration in humans, similar rapid excretion through the urine is

 observed.

 Several oxidized and conjugated metabolites of chlordimeform are

 excreted in the urine, demethylchlordimeform, N-formyl-4-chloro-

 o-toluidine and 4-chloro- o-toluidine being the major metabolites.

 In in vitro studies, the same metabolites are formed,

 4-chloro- o-toluidine being the major metabolite.

 1.6 Effects on laboratory mammals and in vitro test systems

 Chlordimeform has moderate acute toxicity when tested in several

 species by oral and dermal routes of administration. The major

 metabolites have low oral toxicity when tested in rats. Chlordimeform

 causes only slight skin and eye irritation in rabbits. Following

 either short- or long-term exposure in both mice and rats with either

 chlordimeform or its metabolites, treatment-related changes can be

 observed in haematological parameters, and there is some evidence of

 hyperplasia of the epithelium of the bile duct and urinary bladder at

 the high dose levels. Chlordimeform does not cause an increase in

 tumour incidence in rats. In mice, following dietary administration

 of either chlordimeform, N-formyl-4-chloro- o-toluidine or

 4-chloro- o-toluidine, there is a dose-related increase in

 haemorrhagic malignant tumours of vascular origin classified as

 malignant haemangioendotheliomas, which cause a dose-related increase

 in mortality.

 Chlordimeform does not affect reproductive parameters, nor does

 it have any teratogenic potential.

 Chlordimeform has been tested in a broad range of in vitro and

 in vivo genotoxicity assays. No positive responses have been

 reported with any of these tests in which unformulated chlordimeform

 was tested. In addition, there have been several sporadic and

 unconfirmed reports of mutagenic activity induced by N-formyl-

 4-chloro- o-toluidine and 4-chloro- o-toluidine. A single report

 describes cell transformation induction by both chlordimeform and

 4-chloro- o-toluidine. Binding to DNA occurs in the liver of dosed

 mice and rats. One major hydrophobic adduct is found at a much higher

 level in mice than in rats.

 Chlordimeform induces a variety of pharmacological and

 biochemical effects in animals, including cardiovascular changes,

 hypothermia, hyperexcitability, effects on central visual and auditory

 functions, and modulation of biogenic amines and drug-metabolizing

 enzymes.

 1.7 Effects on humans

 Acute poisoning causes fatigue, nausea and loss of appetite, and,

 in more severe cases, somnolence, cyanosis, urgency in urination,

 cystitis, cardiovascular effects (tachycardia, bradycardia, ECG

 changes), coma and shock. Generally, there is complete recovery from

 acute intoxication.

 Following chronic exposure to chlordimeform, additional symptoms

 include abdominal pain, skin itching and rashes (dermal exposure), and

 gross and microscopic haematuria. A large number of cases with

 clinical symptoms of chronic exposure have been reported in both

 chlordimeform-manufacturing plants as well as in agricultural workers.

 Following occupational exposure, epidemiological evidence has

 provided a strong association between exposure to the metabolite

 4-chloro- o-toluidine and the incidence of human urinary bladder

 cancer. There is currently only weak evidence for an association

 between exposure to chlordimeform and human bladder cancer.

 1.8 Effects on other organisms in the laboratory and field

 There were no significant effects on populations of soil fungi,

 bacteria or actinomycetes following application of chlordimeform to

 soil.

 There are no laboratory toxicity data on freshwater

 invertebrates. Growth of larval oysters was inhibited by chlordimeform

 with an EC50 of 5.7 mg/litre. The 96-h LC50 for pink shrimp, the only

 crustacean studied, was 7.1 mg/litre and the 96-h LC50 values for

 fish ranged from 1 to 54 mg/litre. There are no chronic aquatic

 toxicity data available. A mixture of laboratory and field data shows

 that chlordimeform is toxic to a wide range of terrestrial non-target

 arthropods.

 The contact toxicity LD50 for bees has been reported to be

 120 µg/g and that for oral toxicity 187 µg/g. There was no mortality

 in the field following exposure of species of bees to residues on

 alfalfa 3 h after spraying.

 The dietary LC50 for various birds species ranged from >1000 to

 >5000 mg/kg diet.

 1.9 Evaluation of human health risks and effects on the environment

 Heavy exposure during manufacture or use, possibly resulting from

 inadequate safety precautions, has led to signs of acute poisoning in

 workers. Since both production and use are reported to have ceased

 worldwide, acute poisoning should no longer occur. The risk associated

 with chronic exposure, however, particularly the risk of bladder

 cancer, will continue to be of concern for many years. Health

 screening of significantly exposed individuals from manufacturing

 plants from those rural communities where chlordimeform was

 extensively used should be continued.

 Since chlordimeform is no longer used, no quantitative risk

 assessment for the environment has been performed. There are not

 expected to be any long-term detrimental effects on the environment as

 a result of past use of chlordimeform.

 1.10 Conclusions and recommendations

 Chlordimeform has significant potential to cause both immediate

 and long-term toxicity in exposed individuals. Current information

 supports an association between an increased incidence of human

 bladder cancer and exposure to 4-chloro- o-toluidine and, to a lesser

 extent, chlordimeform.

 Chlordimeform does not persist in the environment, and therefore

 there are not expected to be any long-term detrimental effects on the

 environment as a result of past use.

 Future commercial production or use of chlordimeform is not

 recommended. Existing stocks should be disposed of safely.

 Those with occupational exposure to chlordimeform should

 participate in a health screening programme that includes urinary

 cytology and the detection of haematuria.

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

 2.1 Identity

 Common name: Chlordimeform

 Chemical structure:

 

 Chemical formula: C10H13ClN2

 Relative molecular mass: 196.7

 CAS name: N'(4-chloro-2-methylphenyl)-

 N, N-dimethyl-methanimidamide

 IUPAC name: N2-(4-Chloro- o-tolyl)-

 N1, N1-dimethylformamidine

 CAS registry number: 6164-98-3 (chlordimeform)

 19750-95-9 (chlordimeform hydrochloride)

 RTECS number: LQ4375000

 Common synonyms: Chlorphenamidine; chlorfenamidine;

 chlorophedine; chlorophenamide;

 chlorophenamidin; chlorophenamidine;

 N'-(4-chloro- o-tolyl)- N,

 N-dimethylformamidine;

 N, N-dimethyl- N'-(2-methyl-4-

 chlorophenyl)-formamidine;

 N, N-dimethyl- N'-(2-methyl-4-

 chlorophenyl)formadin;

 ENT 27335; ENT 27567; EP-333;

 N'-(2-methyl-4-chlorophenyl)- N,

 N-dimethylformamidine

 Trade names: Acaron; Bellotion Especial; Bermat;

 Bermatchlorfenamidine; C8514; Carzol;

 CDM; CDMS; CGS500; CGS800SP;

 Chlorfenamidine; Ciba 8514; Ciba C8514;

 COTIP 500EC; Fundal; Fundal 500; Fundex;

 Galecron; OMS-1209; Ovatoxion; OVINA;

 OVITIX; RS 141; Schering 36268;

 Sn 36268; Spanon; Spanone;

 SPIKE ULVAIR.

 Technical grade chlordimeform is greater than 95% pure and

 contains the following impurities: N-formyl-4-chloro-2-toluidine

 ( N-formyl-4-chloro- o-toluidine), 4-chloro-2-toluidine

 (4-chloro- o-toluidine hydrochloride) and sodium chloride.

 Chlordimeform free base has been formulated as a 500 g/litre

 emulsifiable concentrate. Chlordimeform hydrochloride has been

 formulated as a 300 or 800 g/kg water-soluble powder, a 20 g/kg dust

 or as 50 g/kg granules.

 2.2 Physical and chemical properties

 Some of the physical and chemical properties of chlordimeform

 base and chlordimeform HCl are shown in Table 1. The molecular

 structure of chlordimeform has been investigated by Gifkins & Jacobson

 (1980) using single crystal X-ray diffraction.

 Table 1. Some physical and chemical properties of chlordimeform

 basea

 Physical state colourless crystalline solid

 Boiling point at 14 mmHg 163 - 165°C

 Melting point 32°C

 Log Kow 2.89

 Vapour pressure at 20°C 48 mPa (3.5 × 10-4 mmHg)

 Density (d30) 1.10

 Solubility in water at 20°C 250 mg/litre

 Solubility in acetone, benzene,

 chloroform, ethyl acetate, hexane,

 methanol at 20°C >200 g/litre

 Half-life at pH 7

 (30°C in water, 5% methanol) 42 h

 Half-life at pH 9

 (30°C in water, 5% methanol) 5 h

 Reactivity Forms salt with acids

 a From: Worthing (1979); IARC (1978)

 Chlordimeform has a solubility in water of 250 mg/litre but is

 readily soluble in organic solvents. It forms salts with acids and the

 hydrochloride salt is readily soluble in water. When pure,

 chlordimeform forms colourless crystals.

 Chlordimeform is a base of medium strength with pKa of 6.8 in

 50% aqueous methanol (Voss et al., 1973) and forms stable salts with

 strong acids.

 Chlordimeform is sensitive to light, especially in alkali, and

 slowly decomposes in neutral and alkaline aqueous solution. The pH

 dependence of photodecomposition of chlordimeform was noted by Su &

 Zabik (1972), who observed that an aqueous solution of chlordimeform

 hydrochloride (pH 3.1) was unaffected by mercury lamp irradiation for

 up to 12 days at 25°C, while a solution of the free base at pH 7-8

 decomposed in the same period to a mixture consisting of N-formyl-4-

 chloro- o-toluidine and a bis-formamidine. Photo-decomposition of

 chlordimeform has also been studied on silica gel chromatographic

 plates with irradiation by long- and short-wave ultraviolet light,

 fluorescent light and sunlight (under glass) for periods of 10 to 20 h

 (Knowles & Sen Gupta, 1969). The major degradation product was again

 N-formyl-4-chloro- o-toluidine with either sunlight or UV light.

 Fluorescent light caused little decomposition. Sunlight resulted in

 12% decomposition in 10 h, while UV resulted in 25% decomposition in

 20 h. When 4-chloro- o-toluidine was irradiated with UV light,

 numerous decomposition products were found but these were not

 characterized further.

 Chlordimeform has relatively high volatility and is thus capable

 of efficient fumigation action. The hydrochloride salt has negligible

 volatility.

 2.3 Conversion factors

 1 ppm = 8.04 mg/m3 1 mg/m3 = 0.12 ppm

 2.4 Analytical methods

 2.4.1 Plants

 Geissbühler et al. (1971) described in detail a method for the

 determination of total residues of chlordimeform and its metabolites,

 which can be used for routine analysis of plant and soil samples. In

 this method, chlordimeform and its metabolites are hydrolysed to

 4-chloro- o-toluidine by successive treatments with acetic acid and

 sodium hydroxide, respectively. The hydrolysis product is then steam

 distilled, extracted with isooctane, diazotized and coupled with

 N-ethyl-1-naphthylamine yielding a purple dye, which, after column

 chromatography on cellulose, is determined by colorimetry. Interfering

 azo-dyes from aromatic plants or soil are removed by chromatography on

 a cellulose column. This colorimetric method has a limit of detection

 of 0.05 mg/kg. If required, the identity of the residues can be

 verified by thin-layer chromatography on a cellulose column. This

 procedure is sensitive to about 0.1 mg/kg. Alternatively, the

 hydrolysis product, 4-chloro- o-toluidine, is diazotized and

 iodinated, and the iodinated derivative is measured by electron-

 capture gas chromatography. This alternative method has a limit of

 detection of 0.05 mg/kg.

 Kossmann et al. (1971) refined the method of Geissbühler et al.

 (1971) to permit separate determination of residue quantities of the

 parent compound and its potential degradation products in plant

 materials. In this procedure, plant material is subject to a two-fold

 extraction, the first with methanol/hydrochloric acid and the second

 with the lipophilic mixture, methanol/methylene chloride. Separation

 of chlordimeform and its degradation products is accomplished by

 thin-layer chromatography. The separated eluants are converted to

 4-chloro- o-toluidine and analysed as described by Geissbühler et al.

 (1971). The limits of detection for the separated compounds,

 chlordimeform, demethylchlordimeform and 4-chloro- o-toluidine are

 0.02 to 0.03 mg/kg.

 Grübner (1977) described a thin-layer chromatographic method for

 the determination of chlordimeform residues alone or together with its

 metabolite, 4-chloro- o-toluidine, in cucumbers and apples. The

 limits of detection for chlordimeform and 4-chloro -o-toluidine were

 0.1 and 0.05 mg/kg, respectively. The rates of recovery were 76-85 and

 90-105%, respectively.

 Fan & Ge (1982) described an alkali flame ionization

 gas-chromatographic method for the determination of chlordimeform and

 three potential metabolites in cargo rice and husk. Residues of

 chlordimeform and its metabolites were extracted with absolute alcohol

 or hexane and cleaned up on neutral alumina columns, before being

 chromatographed in a column of 1% DEGS coated on 60-80 mesh

 405 support (PEG 20M bonded phase). The detection limits for

 chlordimeform, 4-chloro- o-toluidine, 2,2'-dimethyl-4,

 4'-dichloroazobenzene, and N-formyl-4-chloro- o-toluidine were

 0.03, 0.028, 0.11 and 0.43 mg/kg, respectively, for cargo rice and

 0.03, 0.028, 0.22 and 0.43 mg/kg, respectively, for husk. Recovery for

 chlordimeform was 81-93% for cargo rice and 103-104% for husk.

 Recovery for 4-chloro- o-toluidine was 71-73% for both cargo rice

 and husk. Recovery for 2,2'-dimethyl-4,4'-dichloroazobenzene was

 81.8-112% for cargo rice and 109-118% for husk. Recovery for

 N-formyl-4-chloro- o-toluidine was 66% for husk. Mattern et al.

 (1991) described a rapid analytical procedure for 17 pesticides,

 including chlordimeform, using gas chromatography/chemical ionization

 mass spectrometry (GC/CIMS) for detection in various commodities

 including peppers, spinach, lettuce and snap beans. Percentage

 recoveries for chlordimeform were 87.8% (peppers), 72.6% (spinach),

 99.7% (lettuce) and 94.7% (beans). The limits of detection for

 chlordimeform were 0.05 mg/kg (beans), 0.05 mg/kg (lettuce),

 0.05 mg/kg (peppers) and 0.10 mg/kg (spinach).

 2.4.2 Soil

 The method of Geissbühler et al. (1971) described in section

 2.4.1 for plants can equally be applied to the determination of total

 residues of chlordimeform in soil.

 2.4.3 Water

 Machin & Dingle (1977) described a UV spectrographic method for

 the determination of chlordimeform in cattle dipping baths and

 sprays. Preliminary clean-up removes UV-absorbing impurities and

 converts chlordimeform to its hydrochloride. Following silica gel

 chromatography, the absorbance of the non-eluted material is measured

 at 240 nm to determine chlordimeform content. Optimum results are

 obtained in the concentration range of 0.02-0.06% (w/v) chlordimeform.

 2.4.4 Formulations

 Voss et al. (1973) described two methods for the determination of

 chlordimeform in formulations. The first relies on acid titration of

 the free base with hydrochloric acid. The hydrochloride salt is

 converted into the free chlordimeform base, which is extracted into an

 organic solvent. After evaporation of the solvent, the active

 ingredient is determined potentiometrically. The second method makes

 use of gas chromatography, and in this case the chlordimeform

 hydrochloride preparations have to be converted into the base form

 prior to injection into the gas chromatograph.

 Gale & Hofberg (1985) described a gas chromatographic procedure

 for the determination of chlordimeform in emulsifiable concentrate

 formulations. Chlordimeform was extracted with methylene chloride,

 chromatographed on CBWX-20M and detected by flame ionization.

 2.4.5 Air

 There are no published methods described for the determination of

 chlordimeform in air.

 2.4.6 Urine

 Liu & Mao (1980) described a method for the gas chromatographic

 separation of chlordimeform, demethylchlordimeform, N-formyl-4-

 chloro- o-toluidine and 4-chloro- o-toluidine in urine. Optimum

 separation was achieved on a column with 1% polyvinylpyrolidone and 8%

 PEG 20M on 80-100 mesh white diatomeous support no. 101 (acid and base

 washed). The column was suitable for both qualitative and quantitative

 analysis.

 A method to analyse urinary residues of workers occupationally

 exposed to chlordimeform was developed by Ciba-Geigy in 1980

 (Anonymous, 1980a). The method relies on the hydrolysis of

 chlordimeform and other residues to 4-chloro- o-toluidine with sodium

 hydroxide, followed by extraction with hexane and separation on

 reverse-phase liquid chromatography fitted with a UV detector. A

 published version of this method was prepared by Geyer & Fattal (1987)

 in which the alkaline hydrolysate of urine is extracted with hexane,

 the solvent is evaporated, and the hydrolysate is reconstituted with

 aqueous acetonitrile. Separation was performed on a reverse-phase Novo

 Pak 5 mm C18 column with a UV absorbance detector equipped with a 254

 nm filter. A similar method was described by Cheung et al. (1989) for

 the analysis of chlordimeform from urine of field workers. Ross &

 Leisten (1989) have refined this method with the use of synchronous

 spectral data which provides a improved signal-to-noise ratio, which

 gives lower minimum detectable levels while still allowing a

 well-resolved spectrum. This system may allow detection of levels

 equivalent to 1 mg/litre in urine.

 2.4.7 Tissues

 A gas chromatographic method for the determination of residues of

 chlordimeform in animal tissues was first described in the early 1970s

 (Anonymous, 1971a). The method involves hydrolysis of chlordimeform to

 4-chloro- o-toluidine by successive treatments with acetic acid and

 sodium hydroxide. The hydrolysis product is steam distilled and

 extracted into isooctane. Following diazotization of the 4-chloro-

 o-toluidine, the diazo-moiety is exchanged for iodine by potassium

 iodide treatment. The iodinated derivative is gas chromatographed

 using electron-capture detection. The limit of detection using this

 method is 0.02 mg/kg.

 Rieger et al. (1985) have described a gas chromatography/flame

 ionization detection method for the determination of chlordimeform and

 its major metabolite, demethylchlordimeform, from human tissue

 samples, namely, human whole blood and human liver (1:1 aqueous

 homogenate). Tissues were first extracted with an organic solvent,

 transferred to an acid aqueous medium (0.1M hydrochloric acid),

 re-extracted into a small volume of organic solvent and separated on

 GC or GC/MS. Using extraction with either chloroform or n-butanol,

 recoveries of 81 and 75%, respectively, were obtained.

 3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

 3.1 Natural occurrence

 Chlordimeform does not occur naturally.

 3.2 Anthropogenic sources

 3.2.1 Production levels and processes

 Chlordimeform was first commercialized in 1966. It can be

 manufactured commercially by two methods (Voss et al., 1973), both

 starting with the conversion of dimethylformamide to the Vilsmeier

 reagent by reaction with POCl3, SOCl2 or COCl2.

 By the first method, condensation of the Vilsmeier reagent with

 4-chloro-amino-toluene (or 5-chloro-2-aminotoluene, 5-CAT) leads

 directly to chlordimeform hydrochloride. Treatment with a strong base

 gives the free chlordimeform base.

 By the second method, the Vilsmeier reagent is reacted with

 o-toluidine to give phenamidine, which is chlorinated in a second

 step. The chlorination gives rise to a certain amount of isomers as

 unwanted side-products. The crude chlordimeform so obtained has to be

 purified either by recrystallization of its chlorohydrate or by

 rectification of the free base.

 Chlordimeform has been produced at various times in Switzerland,

 Germany, United Kingdom, USA, Italy, Argentina and China.

 Little information is available on the production levels of

 chlordimeform. Information from the US International Trade Commission

 (IARC, 1983) indicated that imports of chlordimeform to the USA

 through the principal US customs districts amounted to 745 tonnes in

 1979 and 198 tonnes in 1980.

 In 1974, total usage of chlordimeform in the USA is estimated to

 have been 590 tonnes, 77% of which was used on cotton, 15% on

 deciduous fruits and nuts, and 8% on vegetables. In 1976, the US

 Department of Agriculture reported that 2000 tonnes of chlordimeform

 was used in the USA on major crops (IARC, 1983). In 1980, total usage

 in the USA was 227 tonnes, all of which was used on cotton to control

 budworm/bollworm.

 Chlordimeform has been used in China throughout the 1970s and the

 1980s at the rate of approximately 10 000 to 15 000 tonnes per year

 (Xue, personal communication). In the Chinese province of Hu-bei, the

 average annual usage during the period 1984-1988 was 3276 tonnes

 (Huang et al., 1989).

 3.2.2 Uses

 Chlordimeform is a broad spectrum acaricide and is active mainly

 against eggs and motile forms of mites and ticks and against eggs and

 early instars of some Lepidoptera insects. It kills eggs, larvae and

 adults not only by contact but also in the vapour phase. The major use

 initially was in the control of mites on deciduous fruit.

 In 1971, chlordimeform products were registered in many countries

 for use on a wide variety of crops such as pome fruits, stone fruits,

 cole crops, vegetables, grapes, hops, citrus, apples, pears, cherries

 and strawberries. Chlordimeform also had important veterinary uses as

 an acaricide. In Australia, chlordimeform was registered for use in

 cattle dips for the control of cattle ticks (Boophilis mictopus), in

 combination with organophosphorus acaricides (FAO/WHO, 1972).

 In 1975, it was reported that the use pattern of chlordimeform

 had been extended to include control of stemborers in irrigated rice,

 control of Lepidoptera larvae on cotton, and control of a wide range

 of Lepidoptera larvae on cabbage and tomatoes (FAO/WHO, 1976). At

 this time, the control of stemborers in irrigated rice proved to be

 one of the most important uses of chlordimeform. In the case of

 cotton, chlordimeform became one of the most important substitutes for

 DDT and other organochlorine pesticides.

 Chlordimeform has had no significant usage in non-crop situations

 other than on ornamentals.

 In 1976, the manufacturers temporarily suspended the sale of

 chlordimeform from all markets worldwide, on the basis of adverse

 carcinogenicity findings in chronic mouse studies.

 In 1978, having completed a number of toxicology, metabolism and

 residue studies, the manufacturers re-applied in a number of countries

 for registration to allow limited commercial use in cotton crops only.

 The proposal was to use chlordimeform by aerial application under

 supervised conditions that limited the uptake by operators and

 by-standers. Chlordimeform was re-introduced for insect control in

 cotton in USA, Central America, Columbia, Israel, Australia and China.

 Guidelines for the handling and use of chlordimeform were set in

 Australia, Columbia, Israel and USA (California). Application rates

 were set to minimize the occurrence of residues in cotton fibres and

 cotton seed oil. In China, extensive use of chlordimeform continued

 through the 1980s on rice and cotton.

 Use of chlordimeform ceased in most countries in the mid to late

 1980. The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) withdrew

 its temporary Acceptable Daily Intake (ADI) in 1987 and recommended

 that chlordimeform should not be used where its residues, or those of

 its metabolite, 4-chloro- o-toluidine, could arise in food. (FAO/WHO,

 1988).

 In 1988-1989, Ciba-Geigy and Schering voluntarily and finally

 halted marketing of chlordimeform and decided to withdraw registration

 worldwide. In China, production stopped at the end of 1992, and sales

 ceased in June 1993.

 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

 4.1 Transport and distribution between media

 4.1.1 Air

 Chlordimeform has relatively high volatility, and thus when

 sprayed on crops considerable evaporation would be expected from plant

 surfaces as well as from the soil. Studies in plants, however,

 indicate a lower rate of evaporation than expected. In bean plants,

 disappearance from the surface in the first few hours was found to be

 of the order of only 30-40% of the original dose applied (FAO/WHO,

 1972). This result was obtained when either chlordimeform or its

 hydrochloride salt was used and is considered to be due to the

 buffering capacity of plant exudates with a resulting equilibrium

 between the free base and salts. The low volatility from plant

 surfaces was confirmed by Sen Gupta & Knowles (1969) on apple

 seedlings and by Ehrhardt & Knowles (1970) on grapefruit seedlings. In

 cotton plants, approximately 55% of the dose applied to leaves was

 volatilized from the surface of the leaves within 2 h (Bull, 1973).

 No studies are available on the volatilization of chlordimeform

 from soil surfaces, but it is likely to be at least as high as from

 leaf surfaces.

 4.1.2 Water

 While chlordimeform base has only low solubility in water, the

 solubility of the hydrochloride salt is relatively high. Its stability

 in water, however, is highly pH-dependent, and in the normally neutral

 to slightly alkaline conditions of rivers and lakes its half-life

 would be relatively short.

 It also has the potential to adsorb readily to dissolved organic

 matter resulting in precipitation (Maqueda et al., 1989).

 The hydrolytic stability of chlordimeform is highly pH-dependent.

 It slowly hydrolyses in neutral pH and is stable in strongly acid

 conditions. The half-life at 10°C is about 38 days at pH 7, compared

 to 8 days at pH 8. At 30°C, these values are reduced to about 3 and

 0.5 days, respectively. A solution of the hydrochloride salt (pH 3-4)

 showed no appreciable hydrolysis over several days (Su & Zabik, 1972).

 The principal product of hydrolysis is N-formyl-4-chloro- o-

 toluidine, which at room temperature is very slowly converted to

 4-chloro- o-toluidine by further hydrolysis. The second step may be

 accelerated by heating with strong acid or alkali.

 4.1.3 Soil

 Hydrolysis of chlordimeform to N-formyl-4-chloro- o-toluidine

 would be expected to be significant under the slightly acid or

 slightly alkaline conditions that normally prevail in soils.

 Despite the reasonably high solubility of the hydrochloride salt

 of chlordimeform, there appears to be little leaching from the site of

 application in the soil (FAO/WHO, 1972).

 In the studies by Fischer & Cassidy on the uptake of

 chlordimeform from soil into cotton plants, the levels of

 chlordimeform in the soil were also analysed (FAO/WHO, 1979). Soil was

 treated when the cotton reached 10 weeks of maturity. Radioactivity in

 the top 75-mm layer of silt loam soil accounted for 1.23 mg/kg

 chlordimeform equivalents after treatment. At 7 weeks, this level had

 decreased to 0.33 mg/kg and at 13 weeks to 0.20 mg/kg. Extraction of

 this layer revealed partition of 32% into the organic layer and 20%

 into the polar fraction, and 44% was non-extractable, indicating rapid

 degradation. For all but one sample, the level of radioactivity as

 chlordimeform equivalents in the lower soil levels, 75-150 mm and

 150-200 mm, was less than 0.01 mg/kg, indicating that leaching did not

 occur in silt loam. In later experiments with regular over-the-top

 spray treatment throughout the maturation of the cotton plants, the

 same rapid decrease in radioactivity (as chlordimeform equivalents)

 was seen in the top 75 mm of soil. Radioactivity in deeper layers was

 again equivalent to less than 0.01 mg/kg. At harvest of the cotton

 plants, up to 91% of the radioactivity in the soil could be converted

 to 4-chloro- o-toluidine.

 The nature of the non-extractable portion of chlordimeform in

 soil was investigated by Perez-Rodriguez & Hermosin (1979) and by

 Hermosin & Perez-Rodriguez (1981) in experiments examining the

 interaction of chlordimeform with clay minerals, montmorillonite,

 kaolinite, illite and vermiculite. The earlier work indicated that the

 adsorption of chlordimeform on clay is essentially a cation-exchange

 reaction and that chlordimeform ions lie between the silicate layers,

 thus being difficult to disperse with water or aqueous solutions of

 inorganic cations. In the later study, chlordimeform adsorption to the

 clay minerals montmorillonite, illite and vermiculite was found to be

 an irreversible process, whereas chlordimeform adsorbed on kaolinite

 is only weakly bonded and easily removed by washing with water.

 The role of soil organic matter in the adsorption and degradation

 of chlordimeform in soil was examined in experiments by Maqueda et al.

 (1983, 1989). In the first study, the interaction of chlordimeform

 with humic acid extracted from the top 20 cm of a clay soil classified

 as Typic Chromozerert soil was examined. Adsorption is essentially a

 cation-exchange process, although other mechanisms, such as charge

 transfer, H-bonding, and van der Waals forces may contribute to the

 high adsorption capacity. The variety of mechanism may make it

 difficult to ascertain the long-term fate in the environment. In the

 second study, the interaction of chlordimeform and other pesticides

 with fulvic acids extracted from a spodosol soil was examined. Fulvic

 acids are the fraction of humic substances that dissolves in both acid

 and alkaline media, and thus are readily found solubilized in lakes

 and rivers. The adsorption of chlordimeform was again shown to be a

 cation-exchange process, together with H-bonding and charge transfer

 mechanisms. Precipitation occurred upon interaction of chlordimeform

 with fulvic acids. The amount of precipitate increased in a

 dose-related manner up to levels of 100 mmol chlordimeform/litre.

 4.1.4 Vegetation and wildlife

 Benezet & Knowles (1981) examined the degradation of

 chlordimeform by two algal types, Chlorella, the green alga,

 and Oscillatoria, a cyanobacterium. In the presence of either

 Chlorella or Oscillatoria, chlordimeform was hydrolysed to

 N-formyl-4-chloro- o-toluidine, probably by a largely non-enzymatic

 reaction. Further reaction formed 4-chloro- o-toluidine and some

 CO2. Oxidative N-demethylation was not a major path for chlordimeform

 degradation by algae.

 The solubility of chlordimeform was sufficient to allow uptake

 by the roots of bean and rice plants and to be transported to

 plant-feeding pests, as demonstrated by the efficacy experiments of

 Dittrich (1967) and Dittrich & Loncarevic (1971).

 The ability of plants to take up chlordimeform from soil was

 further demonstrated by the experiments of Fischer & Cassidy

 (FAO/WHO, 1979), where the soil of a cotton field was treated with

 [14C]-chlordimeform when the cotton was 10 weeks old. Uptake of the

 radioactivity by the cotton plant was noted to occur in small

 quantities, and the highest levels were found in the seeds and fibres.

 Biphasic extraction showed 42% in the organic fraction and 34% in the

 polar fraction, and 24% was not extractable. Thirteen weeks after

 treatment, the mature cotton contained 0.09 mg/kg in the leaves.

 The low level of translocation of chlordimeform in plants was

 demonstrated by Sen Gupta & Knowles (1969) in experiments where

 [14C]-chlordimeform was injected into the stem of apple seedlings

 followed by analysis of stem and leaf radioactivity for a period of 20

 days. For the first 4 days after injection, 95% of the radioactivity

 was localized in the stems, predominantly as the parent compound.

 After 20 days, 71.6% of the radioactivity still remained in the stem,

 with 25.4% in the leaves, and only 17.9% remained as the parent

 compound. The major portion of the radioactivity in the stems after 20

 days was unextractable with chloroform and acetone.

 In the experiments of Ehrhardt & Knowles (1970) with grapefruit

 seedlings, there was no detectable movement of radioactivity into

 adjacent stems and leaves 8 days after application of [14C]-

 chlordimeform to two upper leaves or two lower leaves. Considerable

 movement into stems and leaves was noted when [14C]-chlordimeform was

 injected into the main stem, and also to the periphery of grapefruit

 leaves when it is applied centrally. Thus, movement of chlordimeform

 occurred mainly in the direction of the xylematic transpiration

 stream.

 Application of chlordimeform directly to the leaves of apple

 seedlings (Sen Gupta & Knowles, 1969) or the leaves of grapefruit

 seedlings (Ehrhardt & Knowles, 1970) demonstrated the limited capacity

 of chlordimeform to penetrate the cuticular layers. Ercegovich et al.

 (1972) reported that chlordimeform appeared to adhere to the outer

 surface of fruit and did not appear to translocate readily to the

 fleshy parts. The chief factors which seem to account for the decrease

 of chlordimeform residues in fruit appear to be volatilization,

 weathering and growth dilution.

 Similarly, the application of [14C]-chlordimeform to cotton

 leaves resulted in little movement of radioactivity (and none of

 chlordimeform itself) into the untreated plant parts. The small amount

 of translocated radioactivity consisted exclusively of polar, mainly

 non-extractable substances (Gross, 1977).

 In a field experiment, Fischer & Cassidy treated a cotton field

 plot over-the-top with [14C]-chlordimeform at a rate of 1 kg/ha when

 plants were 12-14 weeks old (FAO/WHO, 1979). Radioactivity in the

 cotton plants immediately after treatment was the equivalent of

 2.44 mg/kg chlordimeform. At harvest, the radioactivity calculated as

 [14C]-chlordimeform was 12.91 mg/kg in the leaves, 0.99 mg/kg in

 the stalks, 0.03 mg/kg in the fibre, and 0.26 mg/kg in the seed, with

 0.07 mg/kg in the oil and 0.19 mg/kg in the meal. Parent chlordimeform

 accounted for 31% and 45.2% in the leaves and stalks, respectively.

 The data indicated that although leaf radioactivity is high, there is

 still little translocation of [14C]-chlordimeform metabolites to the

 seed or fibre.

 Supervised residue trials to determine the residue levels in

 cottonseed and cottonseed products have been conducted (FAO/WHO,

 1979). In general, there is a correlation between the application rate

 and the residue level but the interval between the last application

 and the harvest also has a strong influence on the residue level. The

 decrease of residues with time was most pronounced during the first 10

 days after treatment of the cotton plants. At the maximum application

 rate of 1 kg/ha, the residue level rarely exceeded 2 mg/kg in

 cottonseed, seed meal or crude oil.

 When used for the control of rice stem borer in Japan,

 chlordimeform resulted in low levels of residues in rice grains and

 straws. In rice grain after three treatments, the residue levels of

 chlordimeform, demethylchlordimeform, N-formyl-4-chloro- o-

 toluidine and 4-chloro- o-toluidine were 48, 0.4, 15 and 53 µg/kg,

 respectively. The results indicate a low level of penetration of

 chlordimeform into rice plants. The chlordimeform that entered the

 plant was gradually degraded to 4-chloro- o-toluidine (Iizuka &

 Masuda, 1979).

 There have been no studies conducted on the uptake of

 chlordimeform by wildlife. Studies with experimental animals suggest

 rapid metabolism and excretion, with negligible retention.

 4.1.5 Entry into food chain

 Potential routes of entry of chlordimeform into the human diet

 include the direct consumption of crops containing chlordimeform

 residues, the consumption of processed food prepared from treated

 crops, or the consumption of animal products derived from animals

 treated topically with chlordimeform or raised on chlordimeform-

 containing feed such as cottonseed.

 Since the temporary withdrawal of the use of chlordimeform from

 the market in 1976 in most countries and the later restriction to use

 on cotton, dietary consumption of chlordimeform residues on crops in

 these countries has virtually ceased. However, dietary consumption of

 chlordimeform residues is likely to have continued at least until the

 late 1980s in some areas (see section 5.2.2). The maximum residue

 levels (MRLs) which were used for chlordimeform are discussed in

 section 5.2.2.

 4.2 Biotransformation

 4.2.1 Degradation in plants

 Data reviewed by JMPR (FAO/WHO, 1972) demonstrated that

 chlordimeform was quite rapidly degraded in plants with a high

 inherent metabolic activity (e.g., bean plants) but was only slowly

 degraded in ripe fruits. Green fruits (e.g., grapes) and stems have

 an intermediate rate of degradation of chlordimeform. Tentative

 identification of the observed metabolites indicated that in

 leaves both N'-(4-chloro- o-tolyl)- N-methylformamidine

 (demethylchlordimeform) and N-formyl-4-chloro- o-toluidine were

 major metabolites. In ripe apple and pear fruit, however, only

 N'-formyl-4-chloro- o-toluidine was detected. In all tissues,

 4-chloro- o-toluidine was either not detected or present in small

 quantities, even when six-fold overdose treatment was used.

 In the experiments of Sen Gupta & Knowles (1969), [3H]- or

 [14C]-chlordimeform was applied to apple seedlings by either leaf

 treatment or stem injection. The half-life of degradation was about

 12-16 days, and after 20 days 40% of the radioactivity was still

 unchanged chlordimeform. Organosoluble degradation products were

 identified as demethylchlordimeform, N-formyl-4-chloro- o-toluidine

 and 4-chloro- o-toluidine, with the last two representing less than

 1% of the total radioactivity. Non-extractable radioactivity, possibly

 chlordimeform degradation products complexed with polymeric cell

 constituents, was observed only after stem application.

 In the experiments of Ehrhardt & Knowles (1970), both

 [14C]-chlordimeform and [14C]-chlordimeform hydrochloride were

 applied to the leaf surface of growing grapefruit seedlings. After 20

 days, only 10-20% of total radioactivity was recovered, possibly due

 to evaporation from leaves, and only 1% of radioactivity was unchanged

 chlordimeform. The pattern of metabolites was essentially the same as

 in apple seedlings, but the levels were smaller.

 Witkonton & Ercegovich (1972) examined the metabolites found in

 six different fruits (apples, pears, cherries, plums, strawberries and

 peaches) following treatment at varying rates with chlordimeform.

 Samples of the fruit were collected at various intervals after the

 last application from orchards and plants that had been treated with

 aqueous sprays of chlordimeform. Of the three potential degradation

 products analysed for, only one, namely, N-formyl-4-chloro- o-

 toluidine, was detected, together with the parent compound. The other

 potential degradation products, namely, demethylchlordimeform and

 4-chloro- o-toluidine, were not detected. There was no correlation

 between the amount of chlordimeform and 4-chloro- o-toluidine and the

 application rate or the sampling interval. The nature of the fruit and

 environmental factors were accredited as the major contributing

 factors governing the formation and retention of 4-chloro- o-

 toluidine. At harvest, the total residue in all crops was

 approximately 1 mg/kg, except in peaches, which had approximately

 2 mg/kg of total residue. The chief factors which appeared to account

 for the decrease in chlordimeform residues were weathering and growth

 dilution, rather than chemical or enzymatic degradation.

 The potential formation of azo-derivatives of chlordimeform or

 its metabolite, 4-chloro- o-toluidine, in treated fruit and

 vegetables under field conditions was investigated by Geissbuhler et

 al. (1971) using a sensitive gas-chromatographic residue method that

 allowed the detection of 0.01 mg/kg of 2,2'-dimethyl-4,4'-

 dichloroazobenzene. At 20, 30 or 40 days after a 4-fold overdose

 treatment by chlordimeform to apple fruits and leaves, residues of the

 azobenzene compound were either not detectable or detected at very low

 levels (0.04 mg/kg) in leaves. At normal levels of treatment, residues

 of azobenzene compounds would be unlikely to be detected. This result

 is supported by the experiments of Witkonton (1973), who analysed

 the residues on apple surfaces 60 days after treatment with

 [14C]-chlordimeform. The results of these experiments do not support

 the in vitro studies of Rose (1969a,b), which indicate the potential

 formation of azobenzene derivatives in plants by plant peroxidases.

 The metabolism of chlordimeform in cotton plants was first

 examined by Bull (1973) following treatment of individual leaves with

 [14C]-chlordimeform by petiole injection or by foliar application.

 About 45% of the applied dose was absorbed by the leaves, and the

 balance volatilized from the leaf surface within 2 h. Tentative

 identification of metabolites included demethylchlordimeform,

 N-formyl-4-chloro- o-toluidine and 4-chloro- o-toluidine. After

 1 h, only 2% of the applied dose could be recovered from leaf

 surfaces. The unextractable radioactivity was considered to represent

 decomposition products bound to insoluble plant material.

 Gross (1977) studied the metabolism of [14C]-chlordimeform in

 greenhouse-grown cotton plants following treatment of leaves at a rate

 equivalent to 0.6 kg a.i./ha. Metabolites were extracted into hexane,

 methylene chloride and water-soluble fractions at various times up to

 11 weeks after treatment. The radioactivity in the organic fractions

 consisted of at least seven substances. Four were characterized by TLC

 as chlordimeform, N-demethylchlordimeform, 4-chloro- o-toluidine

 and N-formyl-4-chloro- o-toluidine. Fifty-six percent of the dose

 was found in the plant after one week, the balance being lost by

 volatilization. The main degradation pathway was hydrolysis,

 demethylation only being significant at later sampling times. The loss

 of chlordimeform from the surface of leaves was confirmed by

 Wolfenbarger et al. (1979) who noted that 24 h after cotton leaves

 were treated topically with chlordimeform, only 5% of the EC form was

 recovered, whereas 25% of the HCl salt was recovered.

 Fischer & Cassidy (FAO/WHO, 1979) identified the metabolites in

 leaves after [14C]-chlordimeform was sprayed over-the-top on cotton

 plants. At mature harvest, the radioactivity in the leaves consisted

 of chlordimeform (60.3%), demethylchlordimeform (4.1%), 4-chloro-

 o-toluidine ((7.6%) and N-formyl-4-chloro- o-toluidine (7%). The

 results indicate that the parent chlordimeform will be the major

 chemical residue in the mature cotton foliage.

 Honeycutt & Cassidy (1977) investigated the metabolism of

 chlordimeform in cottonseed following injection of [14C]-

 chlordimeform into the stem of a growing cotton plant. Forty percent

 of the radioactivity in the cottonseed was not extractable. Total

 hydrolysis of the radioactivity in the cottonseed showed that a total

 of 19.8% of the radioactivity could be converted to 4-chloro- o-

 toluidine. The data indicated that the metabolism of chlordimeform in

 cottonseed is extensive and results in conjugation to natural

 products.

 4.2.2 Degradation in soils

 The potential for microbial degradation of chlordimeform in

 the soil was first identified by Johnson & Knowles (1970), who

 demonstrated the capability of several bacteria (Aerobacter

 aerogenes and Serratia marcesens), actinomycetes (Streptomyces

 griseus) and fungi (Fusarium moniliforme and Rhizopus nigricans)

 in culture media to degrade chlordimeform extensively. The

 principal metabolite of the bacterial and fungal species was

 N-formyl-4-chloro- o-toluidine, while for the actinomycete,

 Streptomyces griseus, the principal metabolite was 4-chloro- o-

 toluidine. 4-Chloro- o-toluidine was also formed by the bacteria and

 fungi. None of the microbes formed symmetrical azo-compounds.

 The metabolic fate of chlordimeform in sandy loam over a one-year

 period was examined by Iwan & Goller (1975). Soil samples containing

 2 µCi of either [14C- ring]- or [14C- tolyl]-chlordimeform were

 prepared in an environmental chamber and methanol/benzene extracts

 examined at various intervals. Extractability decreased to 50% within

 7 days and was less than 2% after 360 days. In sterilized soil

 samples, on the other hand, extractability decreased only slowly, and

 70% was still extractable after 180 days. This result indicates that

 microbial activity plays a major role in soil degradation of

 chlordimeform to non-extractable components. Even though bound to

 soil, degradation of chlordimeform continued, as shown by the release

 of CO2 as a consequence of oxidative attack upon the tolyl group.

 Little CO2 was released under anaerobic conditions and no CO2 was

 released from sterile samples. The major pathway of metabolism was

 through hydrolysis to 4-chloro- o-toluidine but oxidative

 N-demethylation was also a significant pathway leading to

 4-chloro- o-toluidine. Further hydrolysis steps followed. The azo

 compound, 2,2'-dimethyl-4,4'-dichloroazobenzene, was formed in small

 amounts only when the initial chlordimeform concentration was

 200 mg/kg in the soil samples. Anaerobic conditions produced the same

 metabolic products with the exception of oxidative products such as

 demethylchlordimeform. The data suggests that even under sterile

 conditions, the degradation of chlordimeform is rapid and its

 half-life in non-sterile soils should not exceed one month.

 In a further study, Iwan et al. (1976) isolated from

 chlordimeform-treated soil four coupling products formed by one-

 electron oxidation of 4-chloro- o-toluidine by soil microorganisms.

 The four products, one of which is 2,2'-dimethyl-4,4'-

 dichloroazobenzene, are formed only from high concentrations of

 chlordimeform (70-100 mg/kg), which are at least 10 times higher than

 the levels occurring after field application.

 4.2.3 Bioaccumulation

 There is no data to indicate that chlordimeform bioaccumulates in

 plant or animal tissues. However, with a low Kow of 2.89, this

 indicates a moderate potential to bioaccumulate.

 4.3 Ultimate fate following use

 Chlordimeform in the air and in water would be expected to

 undergo photodecomposition. In water as well as in soil, chemical

 hydrolysis occurs together with adsorption to organic and clay

 materials. In plants, residues form complexes with polymeric cell

 constituents.

 Chlordimeform can be hydrolysed readily to 4-chloro- o-toluidine

 by heating with alkali. For the disposal of small quantities of unused

 pesticide, the following method is recommended: mix with excess lime

 (CaO) or sodium hydroxide (NaOH) and sand and bury at least 0.5 m

 below the surface in clay soils. Commercial formulations require

 0.5-1.0 kg alkali per kg of pesticide. Alkali can be reduced by 50%

 for dilute formulations, e.g., 1% solution or dust. For very

 concentrated pesticides (> 50% a.i.), double the amount of alkali and

 mix the pesticide with soapy water, before reaction with alkali. Test

 reaction on small scale to discover whether or not it will be too

 vigorous. Larger quantities should be treated in small batches or

 burned in a high-temperature incinerator equipped with effluent gas

 scrubbing (IRPTC, 1992).

 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

 5.1 Environmental levels

 5.1.1 Air and water

 There are no specific data available on the monitoring of

 chlordimeform levels in air and water. In neutral and alkaline

 solutions, relatively rapid degradation would be expected owing to

 hydrolytic instability. Under acidic conditions, slower degradation

 would be expected (Su & Zabik, 1972). Adsorption to organic matter in

 water would also be expected under field conditions. In both media,

 there would be degradation due to photodecomposition (Knowles & Sen

 Gupta, 1969).

 5.1.2 Soil

 Chlordimeform deposited inadvertently on soil surfaces after

 spray application may be expected to dissipate by the following

 processes: volatilization, chemical hydrolysis, photodecomposition and

 microbial degradation. Under field conditions, chlordimeform and its

 4-chloro- o-toluidine-containing metabolites are dissipated according

 to first-order reactions with half-lives ranging from 20 to 40 days

 (Guth & Senn, 1969; FAO/WHO, 1972). The conclusion from these

 experiments is that accumulation of chlordimeform in the soil would

 not be expected.

 Following three applications to rice paddy fields for the control

 of rice stem borer, residues of chlordimeform, demethylchlordimeform,

 N-formyl-4-chloro- o-toluidine and 4-chloro- o-toluidine were

 2900, 9, 190 and 68 µg/kg, respectively, in the top 5 cm of soil, and

 were 150, 1, 8 and 20 µg/kg, respectively, in the 5-10 cm level of

 soil. These results indicate the presence of chlordimeform and its

 degradation products mainly in the upper layer with minimal movement

 downward (Iizuka & Masuda, 1979).

 5.2 General population exposure

 5.2.1 Environmental sources

 There are no longer any environmental sources for exposure of the

 general population to chlordimeform. While chlordimeform was being

 used on cotton, there was potential for general population exposure to

 spray drift from aerial application. The persistence of residues of

 chlordimeform on the leaves of cotton also raised the possibility of

 exposure through contact with the leaves during the growing period or

 during harvesting.

 5.2.2 Residues in raw produce

 Prior to the temporary suspension of its use in 1976,

 chlordimeform was used on a wide variety of crops and on livestock.

 The temporary maximum residue levels (MRLs) shown in Table 2 were

 established at the 1971 meeting of the Joint Meeting on Pesticide

 Residues (JMPR) (FAO/WHO, 1972) as a result of numerous residue trials

 in various countries. Residue trials indicated that whilst there was a

 sharp drop in the residue level between the day of application and the

 second or third day post-treatment, thereafter the rate of decline was

 remarkably slow with a half-life on apples, grapes, pears and tomatoes

 exceeding 21 days.

 Table 2. Temporary tolerances for chlordimeform established in 1971

 (FAO/WHO, 1972)

 Temporary tolerance mg/kg

 Pears, peaches, prunes 5

 Apples, grapes, plums, strawberries 3

 Brassicas, cherries, citrus fruit, cotton seed oil

 (crude and refined), cotton seed 2

 Beans 0.5

 Fat, meat and meat products of cattle 0.5

 Milk (whole) 0.05

 Butter 0.5

 In 1975, the temporary MRL for pears was raised to 10 mg/kg, and

 new temporary MRLs were established for tomatoes (1 mg/kg) and hulled

 rice (0.1 mg/kg) (FAO/WHO, 1976). In 1978, the JMPR meeting retained

 only the MRLs for cottonseed and recommended that for cottonseed oil

 (edible), meat of cattle, pigs, poultry and sheep, and milk and milk

 products no residues should occur at the current limit of detection

 (0.05 mg/kg) (FAO/WHO, 1979).

 The proportion of metabolites and parent compound in the residues

 remaining on fruits at various times after application have been

 determined in numerous trials. In general, the parent compound

 represents the major residue (>80%), followed by N-formyl-4-chloro-

 o-toluidine, N'-(4-chloro- o-tolyl)- N-methylformamidine

 (demethylchlordimeform) and 4-chloro- o-toluidine.

 In Chinese residue trials, chlordimeform residues on green

 cabbage after application by direct spraying of a 800-fold dilution of

 25% chlor-dimeform formulation were 20.9 mg/kg after 4 h, 11.5 mg/kg

 after 2 days, 4.2 mg/kg after 7 days and 0.02 mg/kg after 14 days

 (Anonymous, 1980b).

 In a paper by the Chinese Special Task Group on the residues of

 chlordimeform (Anonymous, 1981), the residues of chlordimeform in rice

 plants during the period 1974-1980 were examined. In the period

 1974-1975, after a single application of 25% aqueous chlordimeform

 (9-11 litre/ha) the residue levels on rice harvested after 33-40 days

 were 0.25-0.28 mg/kg. When applied at half this rate, residue levels

 on rice harvested after 20-74 days were 0.17-0.71 mg/kg. In

 field studies in Beijing in 1977, with the same single rate of

 application, residue levels on rice harvested after 19-42 days were

 0.37-0.51 mg/kg. If 2-3 applications were used, the residue levels on

 rice harvested after 19-31 days were 1.3-1.8 mg/kg. The authors noted

 the difficulty in meeting the requirement for a residue level of

 0.1 mg/kg regardless of the pattern of application. In field studies

 in Hu-bei Province in 1978 with the same application rate, the residue

 levels in rice harvested after 25-42 days were 0.19-1.20 mg/kg. In

 field studies in Zhe-jiang Province in 1978, residue levels in rice

 when harvested after 30 days were 0.080-0.112 mg/kg, while residues in

 rice harvested after 80 days were 0.039-0.100 mg/kg. In field studies

 in Guang-dong Province in 1978, residues in rice harvested after 30

 days were 0.042-0.149 mg/kg. In other field studies in the Guang-dong

 Province in 1980, residue levels on rice harvested after 56 days were

 0.185 mg/kg, but when the harvest was performed at 72 days, the

 residue level was less than 0.10 mg/kg (Anonymous, 1981).

 Huang et al. (1989) reported the residues of chlordimeform on

 both rice and cotton plants in the Hu-bei Province of China between

 1984 and 1988. With 1-3 applications to rice plants, followed by

 harvest after 25-55 days, the chlordimeform residues were generally in

 the range of 0.066-0.820 mg/kg for the rice, 7.70-22.30 mg/kg for the

 husk, and 16.5-21.2 mg/kg for the stem. The authors noted that the

 residue levels seldom met the 1975 JMPR recommended MRL of 0.10 mg/kg

 for hulled rice (FAO/WHO, 1976). In further work on rice plants, it

 was noted that the residue levels for late rice were generally higher

 (approximately 2-fold) in late rice compared to early rice, and that

 the residue levels in both the rice and the husk reduced by more than

 90% when the time to harvest was increased from 26 to 72 days. With a

 72-day harvest, the residue level in the rice was 0.065 mg/kg. The

 residue levels in the stem (18-41 mg/kg), on the other hand, remained

 relatively unchanged over the 72-day period. With 1-3 applications to

 cotton plants, followed by harvest after 40 days, the chlordimeform

 residues were 0.053-0.151 mg/kg in the kernel and 0.118 mg/kg in the

 bracket.

 Chlordimeform residues were also found in 8/15 honey samples

 (Huang et al., 1989). The highest residue found was 32.2 mg/kg, and

 the majority of the samples contained less than half this level. In

 1994 the US FDA collected and analysed samples of honey imported from

 the People's Republic of China. Of 60 samples analysed, 39 had

 detectable residues, the highest being 0.058 mg/kg (Krick, 1994).

 Moore (1971) summarized the results of residue trials on the use

 of chlordimeform as an acaricide in cattle dips in Australia. The

 residues were examined in cattle muscle, fat and liver as well as in

 milk and butter from the first milking. Chlordimeform was used at

 concentrations of 0.0125-0.1% in buffered cattle dips. Residues in

 muscle, fat and liver did not increase greatly with increasing dose

 of chlordimeform, and showed significant reductions between day 1

 and day 3 post-treatment. The maximum residue levels found at day

 3 post-treatment in muscle, fat and liver were 0.33, 0.51 and

 0.69 mg/kg, respectively. At the first milking, the residues levels

 showed a closer relationship with the concentration of chlordimeform

 in the dip. The residue levels in milk and butter at a concentration

 of 0.0125% were 0.01 and 0.30 mg/kg, respectively. The maximum

 residue levels in milk and butter, which were found at the highest

 concentration used (0.2 %), were 0.31 and 1.6 mg/kg, respectively.

 In the study by Burkhard (1971), cows washed with a 0.5%

 solution of chlordimeform to the hindquarters (3 treatments at 7-day

 intervals), had total residue levels in milk, meat and fat below the

 level of detection (0.03 mg/litre), except in milk on the day after

 treatment when the levels rose to 1 mg/kg. In a further study by Voss

 & Burkhard (1971), when cows were fed a concentrate containing

 40-240 mg/kg chlordimeform for periods up to 42 days, the total

 residues of chlordimeform and its metabolites in all milk, meat

 and fat samples were below the limit of detection (0.03 mg/litre or

 mg/kg). In liver and kidney samples, residues rose to a peak between

 14 and 21 days (0.58 mg/kg in liver and 0.13 mg/kg in kidney), which

 was followed by a slow decline.

 In a study by Palmer et al. (1977), residues of chlordimeform

 were determined in tissues and milk of cattle after spray application

 to control cattle tick. In subcutaneous fat from animals sprayed with

 0.45, 0.15 or 0.05% chlordimeform, the residue levels were 2.88, 0.46

 and 0.15 mg/kg, respectively. The half-life of disappearance in all

 cases was 2.46 days. Lower residue levels were found in six other

 tissues, including kidney, muscle and liver. Residue levels in whole

 milk of lactating cows at the three treatment levels were 1.42, 0.28

 and 0.03 mg/litre, respectively. The half-life of disappearance from

 milk was 0.45 days.

 White Leghorn hens fed a laying mash containing chlordimeform at

 levels of 0.25, 0.75 or 1.0 mg/kg were examined for residues in eggs

 and tissues (breast, fat and liver) for periods of up to 28 days. No

 residues were detected in breast meat. Residues were detected in fat

 (0.22 mg/kg) at the 21 days only. Residues in the liver were highest

 between 7 and 14 days (0.20 mg/kg) and reduced rapidly upon withdrawal

 from the chlordimeform-containing feed. There were no detectable

 residues of chlordimeform in eggs (FAO/WHO, 1972).

 Residue trails on cotton were conducted between the years 1969

 and 1978 (FAO/WHO, 1979). The application rates ranged from 0.125 to

 3.6 kg/ha and resulted in mean residue levels of 0.1 to 13.1 mg/kg in

 cottonseed when it was harvested immediately after application. The

 final residue level was dependent on a number of factors including

 application rate, number of applications, and length of waiting period

 before harvest. The application rate had the largest influence.

 5.2.3 Residues in processed food

 Total residues of chlordimeform and its metabolites do not reduce

 substantially during cooking processes, since while the proportion of

 parent compound is reduced, there is an increase in the hydrolysis

 product, N-formyl-4-chloro- o-toluidine. Residues of chlordimeform

 itself in crops decrease through hydrolysis, but volatilization in

 steam during cooking is not an important factor. The rate of

 hydrolysis of chlordimeform is a function of pH and occurs much more

 rapidly in weakly acid or neutral crops such as cauliflower (pH 6) or

 green beans (pH 5) than in strongly acid crops such as apples (pH 2.5)

 or tomatoes (pH 3). These results have been derived from studies in

 different crops such as apples, grapes, tomatoes, cauliflower, beans

 and sugar beet. These studies have also shown that residues of

 chlordimeform and its metabolites are located in the outer parts of

 crops, such as fruit peel. Excessive residues might therefore be

 removed by peeling fruit (apples, citrus) or trimming the outer leaves

 of leaf crops. In general, washing will remove only a small part of

 the total residue (FAO/WHO, 1972).

 Chlordimeform residues in whole apples reduced to approximately

 40% of this level in pressed apple juice, while the level in the wet

 pomace doubled (FAO/WHO, 1972) This is consistent with studies that

 have shown that the residue level in the skin and outer layer is

 approximately 50-fold higher than that found in the flesh (FAO/WHO,

 1972).

 Chlordimeform residues in tea leaves were found to be extractable

 into tea prepared from these leaves to the extent of approximately 50%

 of the total residues (Blass, 1972a).

 Chlordimeform residues in grapes reduced to approximately 60% of

 this level in grape juice (Blass, 1972b). This is consistent with

 studies that have shown that the residue level in the grape skin was

 between 60 and 76% of total residues (FAO/WHO, 1972). Fermentation

 of the grape juice over a period of 72 days yielded a wine that

 contained residue levels similar to those in grape juice (Blass,

 1972c), indicating that the fermentation process does not

 significantly lower the total chlordimeform residue level.

 Chlordimeform residues in green hop cones, when used to prepare

 beer, were found to be reduced to levels below the level of detection

 (0.03 mg/kg) (Voss, 1971).

 Residues associated with the processing of cottonseed have been

 reported (FAO/WHO, 1979). Separation of the cottonseed oil leaves the

 majority of the residues in the hulk and meal, although a significant

 residue still remains in the crude oil. Additional refining processes

 including bleaching, hydrogenating and deodorizing reduce the residue

 level to below the level of detection. Cottonseed oil for human

 consumption is subject to the bleaching and deodorizing processes and

 thus residues of chlordimeform will be virtually zero.

 5.3 Occupational exposure during manufacture, formulation or use

 5.3.1 Exposure during manufacture and formulation

 In the cases described by Folland et al. (1978) of

 hospitalization of three factory workers in the USA who were exposed

 to chlordimeform, the urinary levels of chlordimeform plus 4-chloro-

 o-toluidine were 1.29, 6.32 and 4.85 mg/litre, respectively, three

 days after exposure. This report is described in more detail in

 section 8.2.2.

 In a study on workers in the USA engaged in chlordimeform

 production and packaging in 1976, urine was monitored in more than

 100 workers. In more than 800 individual urine samples, total urinary

 levels ranged from 0.05 to 50 mg/litre (personal communication by J.W.

 Barnett, Ciba-Geigy Agricultural Division, Greenborough, North

 Carolina, USA, to California Department of Food and Agriculture).

 In China, there have been several studies in which the level of

 exposure of workers to chlordimeform in chemical factories has been

 examined together with a medical examination to detect any evidence of

 toxicity in these workers. These are described in section 8.2.

 In the study by Lu et al. (1981), the air concentrations

 in 1974 in a chlordimeform-producing factory were generally below

 0.036 mg/m3, with shorter periods at higher levels (0.108-

 0.33 mg/m3), during specific tasks. Skin contamination on hands and

 forearms was 9.1 mg/h for chemical operators and 964.2 mg/h for

 packers. The urinary excretion levels for chlordimeform and

 4-chloro- o-toluidine in controls were 0.015 and 0.042 mg/litre,

 respectively, in chemical operators were 0.065 and 0.108 mg/litre,

 respectively, and in packers were 0.263 and 0.398 mg/litre,

 respectively.

 In the study by Li et al. (1985b), 24 packers (9 male, 15 female)

 in a chlordimeform manufacturing plant in Jiang-su Province of China,

 were exposed to chlordimeform air concentrations (9 samples over 3

 consecutive days) of 0.066 mg/m3 (range 0.017-0.121 mg/m3). Skin

 contamination of the hands and forearms was 110 µg/100 cm2

 (S.D. 39 µg/100 cm2). Urinary chlordimeform levels were

 0.20 ± 0.13 mg/litre, and urinary 4-chloro- o-toluidine levels

 were 0.48 ± 0.29 mg/litre.

 In a further study (Anonymous, 1985a) in a chlordimeform

 manufacturing factory in China, packers had the highest urinary

 chlordimeform and 4-chloro- o-toluidine levels at 0.39 mg/litre which

 significantly correlated with skin contamination but not with air

 concentration.

 In the study by Tao et al. (1985), 61 employees (25 chemical

 operators, 36 packers) of a pesticide factory in China were exposed to

 air levels in the range 0.074 to 0.160 mg/m3. Skin contamination of

 packers (2.99 mg/day) was higher than for chemical operators

 (0.784 mg/day). The urinary excretion rate of chlordimeform and

 4-chloro- o-toluidine in packers was also higher (0.513 mg/litre)

 than for chemical operators (0.206 mg/litre) or controls

 (0.055 mg/litre).

 5.3.2 Exposure during use

 In a company report by Kossmann (1980), summary data was provided

 on the results of occupational exposure surveillance programmes on

 agricultural workers associated with chlordimeform in nine countries.

 Surveys of aerial pesticide applications to cotton entailed the

 monitoring of about 600 airstrips in 1979 in the nine countries. Over

 28 000 urine samples were analysed from workers in all phases of the

 application situation. The urine was monitored and residue data

 expressed as chlordimeform equivalents. In 1% of the assays,

 substantial chlordimeform urinary residues indicated a significant

 occupational exposure. Over 75% of the samples were at or below the

 lowest level of analytical detection. This report states that, in

 general, the conditions in two countries, the USA and Australia, were

 indicative of favourable working conditions where only about 1% of the

 samples contained a residue level indicating a higher-than-desired

 level of exposure. In a subsequent report by Kenyon et al. (1993),

 however, it is stated that at least 20% of the urine samples in

 agricultural workers associated with chlordimeform in New South Wales,

 Australia, exceeded the maximum permissible exposure level for

 chlordimeform equivalents in urine, which was set at 0.2 mg/litre.

 Operators who exceeded this level were required to be withdrawn from

 the site until the urinary level fell below 0.1 mg/litre. The mean

 sample assays for both ground rig operators and workers involved in

 aerial application exceeded the set level in 1984-1985. Furthermore, a

 number of workers experienced exposures that exceeded the limit on

 multiple occasions. The urine monitoring programme in operation in New

 South Wales, Australia, also grossly underestimated the worker

 exposure levels since its protocol did not allow urine sample

 collection in the first 24 h following potential exposure (Kenyon et

 al., 1993). In the report by Kossman (1980), it is stated that working

 conditions in some other countries (i.e., Colombia, El Salvador,

 Guatemala and Honduras) were less favourable and thus exposure was

 higher. However, in some areas where flagmen were unavoidably exposed,

 the urinary residue levels were low, indicating that with precautions

 exposure can be controlled. In New South Wales and Israel, urine

 monitoring for agricultural workers was mandatory, while in the USA,

 urine monitoring was conducted on a voluntary basis.

 In a report by Henderson (1985), monitoring studies on operator

 exposure during the 1984-1985 cotton season in NSW, Australia, were

 summarized. Urine samples were examined in operators involved in

 application of chlordimeform by both ground-rig (Strong & Bull, 1985a)

 and aerial (Strong & Bull, 1985b) methods. Chlordimeform application

 by ground-rig to 26 444 hectares involved 48 people. A total of 85

 urine samples were examined; in 78.8% of samples the chlordimeform

 level was below 0.20 mg/litre, and in 90.5% of samples it was below

 0.50 mg/litre. The mean sample assay was 0.21 mg/litre. Chlordimeform

 application by aerial spraying to 315 694 hectares involved

 222 people. A total of 919 urine samples were examined and in 80.3% of

 samples, the chlordimeform level was below 0.20 mg/litre, and in 89.8%

 of samples was below 0.50 mg/litre. The mean sample assay was

 0.24 mg/litre.

 The exposure data for chlordimeform used on cotton in seven

 countries (Australia, Columbia, El Salvador, Guatemala, Mexico,

 Nicaragua, USA) for the period 1980-1984 has been compiled in a

 company report by Limmer (1985). Urine samples indicated that in all

 countries, the chlordimeform level was less than 0.3 mg/litre for

 between 70 and 92% of the exposed workers, and was >5 mg/litre in

 less than 2% of workers. The highest levels were recorded in the

 loaders, washers and mechanics, while the lower levels were found in

 the pilots and flagmen.

 In a study by Jiang et al. (1985), exposure of workers engaged

 in spraying chlordimeform with fine mist sprayers in both rice fields

 and cotton fields was examined. The air concentration of chlordimeform

 surrounding the workers during spraying was 0.80 mg/m3. Skin

 contamination from spraying in a rice field was 0.777 mg/100 cm2/h

 (16 samples), and from spraying in a cotton field was 0.445 mg/100

 cm2/h for one group (40 samples) and 1.216 mg/100cm2/h for a

 second group (40 samples). Urinary excretion of chlordimeform and

 4-chloro- o-toluidine together was 0.756 mg/litre for rice workers,

 and 0.490, 0.465 and 1.125 mg/litre in three separate groups (40 each)

 for cotton workers. Good correlation was noted between skin

 contamination and urinary excretion. It was noted that contamination

 of the lower extremities of the body was significantly different

 between workers with protection (0.490 mg/100 cm2 per h) and those

 without (1.179 mg/100 cm2 per h).

 In a study by Ling et al. (1986) and Zhang et al. (1986a),

 excretion of chlordimeform and 4-chloro- o-toluidine was examined as

 a measure of occupational exposure. Chlordimeform applicators (7 male,

 6 female; 20-41 years) were examined during spraying of cotton for

 three consecutive days for 4.7, 3.0 and 4.4 h respectively in July

 1985. Protective measures included gauze mask, plastic gloves and

 plastic apron, although it was noted that extensive contamination

 occurred. Air levels in the breathing zone on each of the three days

 were 0.011, 0.014, 0.011 mg/m3, respectively. Skin contamination on

 each of the three days was estimated by the method of Zhang et al.

 (1986b) to be 10.99, 4.32, and 4.45 mg/day, respectively. Urinary

 chlordimeform and 4-chloro- o-toluidine together were measured over

 the 3 days of exposure and for 7 days after cessation of exposure.

 Urinary levels ranged from a peak of 2.408 mg/litre during exposure to

 0.036 mg /litre after 7 days. Excretion of chlordimeform occurred very

 rapidly and the highest level was detected in the sample collected at

 the end of each shift. There was a close correlation between skin

 contamination and urinary excretion. Metabolism occurred very rapidly

 since 4-chloro- o-toluidine usually accounted for 70-93 % of the

 total amount in the urine. The authors concluded that the level of

 urinary chlordimeform plus 4-chloro- o-toluidine is an accurate index

 of chlordimeform exposure.

 Maddy et al. (1986) reported the results between 1982 and 1985 of

 a programme of monitoring the urine of more than 200 workers who had

 received training in the use of chlordimeform on cotton in California.

 Protective clothing was required for all employees who handled

 containers, prepared mixtures, loaded application vehicles, applied

 chemical, flagged or did repair work on equipment exposed to

 chlordimeform. This included cloth overalls, washable hat, waterproof

 boots, waterproof gloves, and a full-face shield. Chlordimeform was

 detectable in urine as early as 4 h after dermal exposure, but did not

 increase during the work season. The chlordimeform concentrations

 averaged about 90 µg/litre, with the highest levels found in

 mixer-loaders and somewhat less in equipment washers, and the lowest

 levels in pilots and flaggers. Urinary levels in the 8-10 h following

 a work shift gave a good indication of exposure for the shift just

 completed.

 Kurtz et al. (1987) reported the results of a monitoring

 programme of agricultural workers exposed to chlordimeform when used

 on cotton in Imperial Valley, California, during the 1982 season. More

 than 1000 urine samples were taken from 132 workers, including pilots,

 mixers/loaders, flaggers and equipment maintenance workers.

 Chlordimeform metabolites were detected in all workers at some time

 during the study despite the use of protective clothing. The level of

 urinary metabolites was positively correlated with the length of

 exposure and the nature of job activity as shown in Table 3.

 Mixer/loaders and maintenance workers had the highest levels.

 Metabolites appeared in urine within 4 h and approximately 75% of

 urinary excretion occurred within the first 24 h.

 Table 3. Chlordimeform metabolite concentrations in urine (mg/litre)

 of agricultural workers during an 11-week application period

 (Kurtz et al., 1987)

 Work group Immediately post-work Following morning

 No. Mean SD No. Mean SD

 All groups 535 0.12 0.41 572 0.10 0.23

 Pilots 145 0.08 0.10 163 0.08 0.10

 Mixers/Loaders 156 0.19a 0.71 162 0.15b 0.36

 Flaggers 202 0.07 0.08 213 0.07 0.09

 Others 32 0.25 0.45 34 0.21c 0.36

 a Significantly greater versus flagger group (P<0.01)

 b Significantly greater versus pilots (P<0.01) and flaggers

 (P<0.001)

 c Significantly greater versus pilots (P<0.001) and flaggers

 (P<0.001)

 Lemesch et al. (1987) provided the results of monitoring for

 chlordimeform exposure in agricultural workers in Israel during

 1980-1985. Chlordimeform was used only on cotton by aerial application

 and all workers were monitored for urinary chlordimeform and its

 metabolites on a weekly basis. The results indicated 86.8% of the

 urine samples contained less 0.05 mg/litre, and 1.4% contained more

 than 0.30 mg/litre. Overall, the loaders had the highest exposure

 followed by the mechanic and then the pilots (see Table 4).

 Table 4. Chlordimeform metabolite concentrations in urine (mg/litre)

 of agricultural workers in Israel during 1980-1985

 according to occupation (Lemesch et al., 1987)

 Occupation < 0.05 0.05 - 0.30 > 0.30 Total

 No. % No. % No. %

 Loaders 666 79.0 157 18.6 20 2.4 843

 Mechanics 383 94.8 19 4.7 2 0.5 404

 Pilots 287 98.2 5 1.7 - - 292

 Total 1336 86.8 181 11.8 22 1.4 1539

 Balu (1989) has provided the results of monitoring field worker

 exposure to chlordimeform from aerial application on cotton. During

 the years 1978-1984, urine samples using a grab sample technique from

 approximately 4600 field workers were examined. For mixer/loaders,

 between 0.5 and 1.9% had levels >5 mg/litre, and between 2.1 and 18%

 had levels of 1.0-5.0 mg/litre. The majority (46-78%) had levels in

 the range <0.05-0.10 mg/litre. There was no apparent change in the

 proportion of workers in the various exposure levels over the course

 of the study. For the pilots, between 0.3 and 0.7% had levels

 >5.0 mg/litre, while 63-90% had levels between <0.05 and

 0.10 mg/litre.

 The clinical signs associated with chlordimeform exposure in

 these studies are described in section 8.2.2.

 6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

 6.1 Absorption, distribution and excretion

 6.1.1 Mouse and rat

 The earliest investigations on the kinetics and distribution of

 chlordimeform were performed in a series of studies on rats (FAO/WHO,

 1972). Four male and four female rats were treated orally with 270 µg

 [3H-phenyl]-chlordimeform. Over a 24 h period, 52.8% (range

 41.8-59.6%) of the radioactivity was eliminated in urine and 2.5%

 (range 0.13-5.30%) in faeces, while 19-23% of the dose was excreted

 into the bile. Following intravenous injection of 270 µg [3H-phenyl]-

 chlordimeform in rat, elimination of radioactivity over 24 h consisted

 of 53.7% (range 52.0-55.6%) in urine and 1.42% (range 1.19-1.84%) in

 faeces.

 Oral dosing of male rats with 270 µg [3H-phenyl]-chlordimeform

 resulted in residues in liver (0.78 mg/kg), kidney (0.59 mg/kg)

 and lymph nodes (0.35 mg/kg) after 8 h. After 24 h, residues in

 gastrointestinal tract (and contents) and liver were 0.95 and

 0.35 mg/kg, respectively. All other tissues contained residue levels

 of <0.16 mg/kg at 8 h, and <0.27 mg/kg at 24 h (FAO/WHO, 1972).

 Oral dosing of male rats with 270 µg [3H-phenyl]-chlordimeform

 for seven consecutive days resulted in excretion of 59% of the

 administered label in urine and 10% in faeces during the dosing

 period. Tissue residues at the termination of dosing were less than

 0.03% of the administered dose (FAO/WHO, 1972).

 Knowles & Sen Gupta (1970) further studied the toxicokinetics

 in rats. A group of two male and two female rats was given

 [14C-tolyl]-chlordimeform (3 µCi) orally (dose unspecified). Over a

 72-h period, 88% of the administered radioactivity was eliminated in

 the urine, with the highest concentration occurring at 12 h, and 7.5%

 was eliminated in the faeces. At sacrifice (72 h), tissue levels based

 upon [14C]-label levels were 0.21 mg/kg in liver, 0.15 mg/kg in

 muscle, 0.11 mg/kg in fat and less than 0.1 mg/kg in other tissues. As

 part of the same study (Knowles & Sen Gupta, 1970), a similar group of

 male and female rats received an oral dose of [14C-methyl]-4-chloro-

 o-toluidine. Tissue levels based upon [14C]-label levels at 72 h

 after dosing were 0.33 mg/kg in fat, 0.26 mg/kg in liver, 0.2 mg/kg in

 kidney and oviduct, 0.1 mg/kg in brain, and less than 0.1 mg/kg in

 other tissues.

 In a more recent study by Watanabe & Matsumura (1987) concerning

 the comparative metabolism of chlordimeform and sulfamidine in rats,

 it was found that after administration of [14C]-chlordimeform as a

 single oral dose (130 mg/kg), radioactivity was eliminated in the

 urine (87%) and faeces (8%) within 3 days. Most of the radioactivity

 was excreted within 2 days. After 5 daily doses of [14C]-

 chlordimeform (26 mg/kg), 78% of the radioactivity was excreted in the

 urine and 15% in the faeces. After 10 days, the residue level in all

 tissues, except blood and liver, was below 1 mg/kg.

 In a study by Ifflaender (1977a), groups of mice (8/sex; strain

 Tif:MAG f) and rats (3/sex; strain TIF:RAI f) were administered

 [14C- ring]-chlordimeform orally at a dose of 25 mg/kg body weight.

 The general excretion pattern was similar for both mice and rats with

 more than 70% of the [14C]-label being excreted within 24 h. Of the

 excreted dose, 80-95% was excreted through the urine, while 10-15% was

 excreted through the faeces. After 144 h, 95-113% of the administered

 dose was recovered. Over the period of the experiment (144 h), the

 levels of radioactivity in the urine were found to range from 82-97%

 of the administered dose. Residues of chlordimeform were found in

 liver, kidney and blood, with the highest level found to be 1 mg/kg.

 Slightly higher residue levels were found to be present in females

 than in males. In a subsequent study by Ifflaender (1977b) to

 determine the quantitative differences between mice and rats, animals

 were administered 25 mg/kg body weight [14C- ring]-chlordimeform.

 Rapid urinary excretion of chlordimeform was again observed in both

 mice (85%) and rats (75%) within 24 h.

 In a more detailed toxicokinetic study by Kopp et al. (1977),

 chlordimeform was administered orally to female mice at two dose

 levels (1.2 or 120 mg/kg body weight) using either a single acute or

 multiple daily administration for up to 21 days. The results again

 indicated rapid excretion of chlordimeform and/or its metabolites

 through the urine and did not provide any indication of

 bioaccumulation at either dose level. At the high dose level, a

 slightly reduced 24-h excretion pattern of the radioactivity was

 observed following a single administration. This pattern returned to

 normal within two to three doses in the multiple dosing regime. The

 percentage of excretion was the same after a period of 21 days,

 irrespective of the dose level. The authors concluded that

 chlordimeform excretion was largely complete within 24 h of

 discontinuation of administration. No accumulation of residues was

 evident.

 Knowles & Benezet (1977) studied the kinetics of chlordimeform in

 mice following intraperitoneal injection of 0.6 µCi [14C-tolyl]-

 chlordimeform. Over the 96-h period, 95.5% of the administered dose

 was eliminated, with 42.5% in the urine and 53% in the faeces. In the

 first 3 h, 43.7% was eliminated, with 27.3% in urine and 16.4% in

 faeces.

 In a study in mice by Crowder & Whitson (1980), the excretion and

 retention of [14C]-chlordimeform in mice was found not to be affected

 by oral co-administration of toxaphene or methyl parathion. Low

 residue levels of chlordimeform were evident at 196 h in all tissues

 following oral administration.

 6.1.2 Other species

 In a study by Sen Gupta & Knowles (1970), two female dogs (18 and

 20 kg) were given 10 µCi [14C]-chlordimeform as a single oral dose

 (0.3 mg/kg), and one male dog (12 kg), which had undergone cannulation

 of the gall-bladder and ligation of the bile duct, was given 20 µCi

 [14C]-chlordimeform orally. Urine was collected (by catheterization)

 at 1, 3, 6, 12, 24, 48 and 72 h. Faeces were collected at similar time

 intervals. Of the administered [14C] label, 85% was recovered in

 urine, 0.6% in faeces, and 5% in the bile within 72 h. In the same

 study, two brush goats, a male (36 kg) and a lactating female (39 kg)

 were administered 10 µCi [14C]-chlordimeform orally. The male goat

 eliminated 87% of the administered dose through the urine within 48 h,

 while the lactating female eliminated only 67% during the same period.

 Only about 0.3% of the applied dose was eliminated in the milk within

 96 h.

 In a review by Knowles (1970), the metabolites found in three

 species, namely, rat, dog and goat, were compared. In all three

 species, oral treatment with radioactive chlordimeform resulted

 primarily in elimination through the urine. Cumulative percentages of

 the dose excreted in the urine 24 h after treatment were 85% for rats,

 70% and 80% for the two dogs, 65% for a lactating goat, and 80% for a

 male goat. Rats eliminated 7.5% of the dose in the faeces by 72 h, and

 only 0.6% and 1.8% of the administered radioactivity was accounted for

 in dog and goat faeces, respectively. The rate of degradation of

 chlordimeform was also different in the three species. By 24 h after

 treatment, 25% of the radioactive material in rat urine was

 organosoluble and partitioned into chloroform, but in the dog and goat

 urine less than 10% was organosoluble. Levels of chlordimeform

 expressed as percentages of organosoluble urinary radioactivity at 24

 and 72 h post-treatment were 9.9 and 2.1% for the rat, 1.3 and 0.2%

 for the dog, and 0.1 and <0.1% for the goat.

 6.1.3 Human

 In a study by Nixon & Neal (1983), the excretion of chlordimeform

 residues was examined in eight volunteers following dermal

 application. A dose of 24.75 mg chlordimeform was applied to the

 forearm via a patch which was removed after 4 h and the application

 site washed in propanol followed by detergent. The average absorbed

 dose was calculated to be 7.95 mg. Urine was collected for 72 h

 following treatment. During this period, an average of 38.3% of the

 absorbed dose was recovered from the urine. The half-life for

 excretion was between 5.9 and 12.1 h, with an average of 8.8 h.

 A number of studies have been conducted that monitored the urine

 of workers exposed to chlordimeform during use (see section 5.3.2).

 The data indicate rapid metabolism of chlordimeform to 4-chloro- o-

 toluidine, followed by urinary excretion. Detection in the urine was

 as early as 4 h after exposure, and approximately 75% was excreted

 within 24 h.

 6.2 Metabolic transformation

 6.2.1 Mouse and rat

 In an early study (FAO/WHO, 1972), the urine from a male rat

 collected over 72 h subsequent to oral administration of 1.1 mg

 [3H-phenyl]-chlordimeform contained free extractables representing

 22% of the [3H] label, of which 10% was in the water phase and 17%

 was extractable glucuronides. The free extractable [3H]-label

 comprised chlordimeform, 4-chloro- o-toluidine, N-formyl-4-chloro-

 o-toluidine, and N'-(4-chloro- o-tolyl)- N-methylformamidine

 (demethylchlordimeform). Glucuronides were based on the same compounds

 found as free extractables.

 In a study by Knowles & Sen Gupta (1970), pairs of male and

 female rats were treated orally with 3 µCi [14C-tolyl]-chlordimeform.

 Urine and faeces were collected at 3, 12, 24, 48 and 72 h after

 dosing. Urinary and faecal elimination of [14C] label after 72 h

 comprised 88% and 7.5% of the administered dose of [14C]-

 chlordimeform, and 71 and 24.5% of the administered [14C]-4-

 chloro- o-toluidine. Chloroform extraction removed 30% of the

 radioactivity from the urine of [14C]-chlordimeform-treated rats, the

 extract containing chlordimeform, N'-(4-chloro- o-tolyl)-

 N-methylformamidine (demethylchlordimeform), N-formyl-4-chloro-

 o-toluidine, and 4-chloro- o-toluidine, in addition to three

 unidentified metabolites. A considerable amount of radioactivity

 remained at the point of origin of the chromatograph, with the amount

 remaining increasing with time, (30% at 3 h and 75% at 72 h). At 3 h,

 the four identified compounds were present in approximately equal

 amounts. By 12 h, the level of N'-(4-chloro- o-tolyl)- N-

 methylform-amidine had decreased to approximately 25% of the level of

 any of the other three compounds. By 48 h, chlordimeform levels were

 half those of the other two compounds, and, by 72 h, N-formyl-

 4-chloro- o-toluidine was present in the greatest proportion.

 As part of the same study (Knowles & Sen Gupta, 1970), a similar

 group of male and female rats received an oral dose of [14C-methyl]-

 4-chloro- o-toluidine. The metabolites found in ethyl acetate-

 extracted urine comprised 5-chloroanthranilic acid, and N-formyl-

 5-chloroanthranilic acid increased. The level of 5-chloroanthranilic

 acid remained constant. A large amount (20-50%) of the radioactivity

 remained at the origin of the chromatograph. Five unidentified

 compounds were noted.

 The metabolic transformation of the metabolite

 demethyl-chlordimeform ( N'-(4-chloro- o-tolyl)- N-

 methylformamidine) in the rat was investigated by Benezet & Knowles

 (1976). Eight Sprague-Dawley rats were each administered 1.5 µCi

 [14C]-demethylchlordimeform by oral intubation. Urine and faeces were

 analysed over a 72-h period. The majority of the radioactivity was

 eliminated through the faeces (64%) but significant amounts were also

 eliminated in the urine (35%). The peak level of radioactivity

 occurred in the urine between 12 and 24 h, and in the faeces between

 18 and 48 h. Of the urinary radioactivity, 16-26% could be extracted

 with ethyl acetate. Compounds present included demethylchlordimeform,

 N'-(4-chloro- o-tolyl)formamidine, N-formyl-4-chloro- o-

 toluidine, 4-chloro- o-toluidine and several unidentified compounds.

 The aqueous fraction remaining after ethyl acetate extraction (74-85%

 of the total radioactivity) was largely acid-labile and probably

 consisted of conjugates, possible glucuronides and ethereal sulfates.

 Approximately 25% of the total radioactivity of the faeces was

 extractable with ethyl acetate, and similar metabolites were present.

 Ifflaender (1977b) examined the quantitative differences in

 urinary metabolites between mice and rats following oral

 administration of [14C]-chlordimeform at a dose level of 25 mg/kg

 body weight. Little quantitative difference in individual

 metabolites was observed between the species. Of the total

 metabolites, N'-(4-chloro- o-tolyl)- N-methyl formamidine

 (demethylchlordimeform) represented 11.3% in rats and 2.4% in mice,

 while 4-chloro-2-methyl-phenylurea represented 6.3% in rats and 1.2%

 in mice. Sulfuric acid conjugates represented 20.8% in mice compared

 to 14.0% in rats. Glucuronic acid conjugates (representing 28% of

 metabolites) and all other minor metabolites were in similar amounts

 in the urine of rats and mice. Acid hydrolysis of the urine released

 degradation products in similar amounts in the urine of rats and mice.

 Knowles & Benezet (1977) reassessed the metabolism of

 chlordimeform in rat and also assessed the metabolism in mice. Ten

 male rats were treated orally with 2 µCi [14C]-chlordimeform and

 urine samples collected at 12 and 24 h. Twelve male mice were injected

 intraperitoneally with 0.6 µCi [14C]-chlordimeform, and urine and

 faeces samples were collected at various times up to 96 h. In rat

 urine, the major organosoluble metabolites (>10%) included

 3-(4-chloro- o-tolyl)urea, N-formyl-4-chloro- o-toluidine,

 4-chloro- o-toluidine, and N-formyl-5-chloroanthranilic.

 Demethylchlordimeform, didemethylchlordimeform, 1,1-dimethyl-3-

 (4-chloro- o-tolyl)urea and 5-chloroanthranilic acid were minor

 metabolites. In mouse urine, the majority of the radioactive material

 was water soluble, probably consisting mainly of conjugates such as

 glucuronides and ethereal sulfates (based on analogy with metabolism

 in rats). The major organosoluble metabolites (>10%) were

 N-formyl-4-chloro- o-toluidine, 4-chloro- o-toluidine and

 N-formyl-5-chloroanthranilic acid. The minor metabolites identified

 in rat urine were also present in mouse urine. The identity of the

 major metabolites in rat urine were confirmed in the study of Watanabe

 & Matsumura (1987).

 Knowles & Benezet (1977) proposed the metabolic pathway for

 chlordimeform metabolism in rats and mice shown in Fig. 1.

 6.2.2 Other species

 In the study of Sen Gupta & Knowles (1970) in dogs described in

 section 6.1.2, chloroform extraction of the urine removed 10% of the

 radioactivity. Thin-layer chromatography of the extract revealed

 chlordimeform, N'-(4-chloro- o-tolyl)- N-methylformamidine

 (demethyl-chlordimeform) and 4-chloro- o-toluidine in about equal

 quantities, but about four times as much N-formyl-4-chloro- o-

 toluidine at 1 h after treatment. The level of unchanged chlordimeform

 and N'-(4-chloro- o-tolyl)- N-methylformamidine decreased steadily

 with time, whereas 4-chloro- o-toluidine and N-formyl-4-chloro- o-

 toluidine rose to maximum levels between 6 and 12 h prior to tapering

 off. Three unidentified metabolites were present. In addition, a lot

 of the radioactivity remained at the origin of the chromatograph.

 Re-runs of this material in polar solvents showed 5-chloroanthranilic

 acid, N-formyl-5-chloroanthranilic acid and three unidentified

 compounds were present. Some radioactivity still remained at the

 origin. The urinary [14C] label not extracted by chloroform was

 treated with enzymes (œ-glucuronidase, œ-glucu-ronidase-aryl

 sulfatase) to form "aglycones". About 75% of the remaining [14C]

 label was extracted in this manner (hydrochloric acid released 62%),

 and thin-layer chromatography showed the same compounds as found in

 the chloroform extract, the major metabolite being N-formyl-

 4-chloro- o-toluidine. In addition, more of one of the unidentified

 metabolites was present. Again re-chromatography of the 45% of the

 radioactivity remaining at the origin with more polar solvents

 revealed 5-chloroanthranilic acid to be the major product. In the

 bile, peak concentration of radioactivity occurred at 8 h. About 10%

 of this activity could be partitioned into ether, and thin-layer

 chromato-graphy of the extract indicated the same four compounds seen

 in urine chloroform extract. N'-(4-chloro- o-tolyl)- N-

 methylformamidine (demethylchlordimeform), N-formyl-4-chloro-

 o-toluidine and an unidentified compound accounted for most of the

 activity at 2 h. By 6 h, 75% of the activity was due to N-formyl-4-

 chloro- o-toluidine. Incubation of extracted bile with enzymes or

 acid gave the same "aglycone" compounds as found in urine. Tissue

 residues of [14C] label at 72 h ranged from 72 µg/kg in liver to

 30 µg/kg (kidney), 13.5 µg/kg (lung), 11.9 µg/kg (spleen and brain)

 and 5 µg/kg (heart and fat and pancreas).

 

 In the same study, metabolites extracted from goat urine were

 analysed by thin-layer chromatography. The major urinary metabolite

 was N-formyl-4-chloro- o-toluidine. The metabolites in goat urine

 showed a similar pattern to those in rats, with a similar proportion

 of conjugated material.

 The comparative metabolic fate of chlordimeform in rats, goats

 and dogs is considered in a review by Knowles (1970), which emphasizes

 the similarity between these species.

 6.2.3 In vitro studies

 Initial studies on the in vitro metabolism of chlordimeform

 were conducted with [3H-phenyl]-chlordimeform (FAO/WHO, 1972).

 Incubation of [3H-phenyl]-chlordimeform for 120 min with rat liver

 homogenate resulted in 24% unchanged chlordimeform, 45% 4-chloro- o-

 toluidine, and 11% unidentified metabolites being formed. Rabbit liver

 homogenate yielded 53, 40 and 7% of the same metabolites,

 respectively. Incubation of 60 µg [3H-phenyl]-chlordimeform (30 µCi)

 with 5 ml human plasma yielded N-formyl-4-chloro- o-toluidine only.

 Conversion was 25% in 5 h, and 50% in 20 h. Rose (1969a) confirmed the

 rat liver homogenate studies using [14C]-chlordimeform. Three

 unidentified metabolites were also observed and, in addition,

 chlordimeform degradation was shown to require the presence of

 nicotinamide. Spleen homogenates were inactive with regard to

 chlordimeform degradation.

 The metabolism of chlordimeform in vitro was first reported by

 Ahmad & Knowles (1971). Incubation of [14C]-chlordimeform with

 various rat liver enzyme preparations identified demethylchlordimeform

 as the major metabolite, which was formed by microsomal

 N-demethylase in the presence of exogenous nicotinamide. This

 reaction was inhibited by mixed function oxidase inhibitor, SKF-525A.

 The chlordimeform metabolites formed in vitro were qualitatively

 similar to those detected in urine from chlordimeform-treated mammals.

 This has been confirmed by others (Hill et al., 1979; Ghali

 & Hollingworth, 1985; Kimmel et al., 1986; Watanabe & Matsumura,

 1987).

 Knowles & Benezet (1977) confirmed that the major in vitro

 metabolite was demethylchlordimeform, but also found that

 N-formyl-4-chloro- o-toluidine and 4-chloro- o-toluidine were

 present in appreciable amounts.

 Ahmad & Knowles (1971) also investigated the metabolism of

 [14C]- N-formyl-4-chloro- o-toluidine) in the presence of rat liver

 enzyme preparations. Eighty percent of this metabolite was metabolized

 by an enzyme, probably a hydrolase, in the soluble fraction, with

 major metabolites being 4-chloro- o-toluidine (52%) and an unknown

 substance (26%).

 The question of the possible formation of azo-derivatives in

 animal tissues was investigated by Rose (1969a). A number of

 experiments were conducted to investigate the presence or absence of

 azobenzene formation from chlordimeform or 4-chloro- o-toluidine. In

 the first experiment, it was demonstrated that peroxidase activity was

 negligible in rat liver and spleen. Furthermore, catalase, which was

 abundant in the same tissues, and which, like peroxidase, catalyses

 reactions between hydroxyperoxides and many oxidizable compounds, was

 shown to be unable to form symmetrical azo-derivatives from

 4-chloro- o-toluidine. In the second experiment, it was demonstrated

 that rat liver and spleen homogenates, which were fortified with

 nicotinamide, and which degrade chlordimeform to demethylchlordimeform

 and small quantities of N-formyl-4-chloro- o-toluidine and

 4-chloro- o-toluidine, respectively, did not form any azobenzene

 derivatives. These compounds therefore do not represent metabolites of

 chlordimeform or its aromatic amine degradation products in animal

 tissues.

 Lin et al. (1975) have investigated the metabolism of

 chlordimeform in primary embryonic lung cell cultures. In 2 h of

 incubation, 97% of chlordimeform was metabolized to N-formyl-4-

 chloro- o-toluidine (81.9%) and 4-chloro- o-toluidine (2.3%). The

 route of metabolism, which was different to that seen in mammals,

 appeared to be first demethylation followed by cleavage at the

 carbon-nitrogen double bond to form N-formyl-4-chloro- o-toluidine.

 The formation of the demethylchlordimeform was minute compared to that

 of the N-formyl derivative. The minor metabolites observed were

 demethylchlordimeform and two unknown metabolites. When incubated in

 culture media without cells, chlordimeform decomposed to

 N-formyl-4-chloro- o-toluidine.

 7. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

 7.1 Single exposure

 7.1.1 Oral

 The acute oral toxicity data for chlordimeform is presented in

 Table 5 and for chlordimeform hydrochloride in Table 6.

 The general signs of toxicity in rats are hyperactivity,

 dyspnoea, muscular weakness, tremors, "Straub's tail", spasms,

 convulsions and respiratory arrest. No pathological changes were noted

 in the rat following oral treatment.

 In mice, signs of toxicity were similar, but some differences

 were noted. Symptoms included restlessness, hyperreflexia and tremors,

 particularly of the head and forelimbs, that developed to one or more

 episodes of clonic convulsions. Death usually occurred within one hour

 during one of the convulsive episodes. If the animal survives this

 hyperexcitation and tremor, it becomes sedated, locomotion is

 suppressed, and it usually recovers within 24 h.

 The acute oral toxicity data for metabolites of chlordimeform is

 presented in Table 7.

 7.1.2 Other routes

 The acute dermal toxicity data for chlordimeform in rats is

 presented in Table 5 and for chlordimeform hydrochloride in Table 6.

 The base, but not the hydrochloride, is readily absorbed by the skin

 (Knowles, 1991). The general signs of toxicity are dyspnoea,

 exophthalmos, prostration, spasms and convulsions. Pathological

 changes in the rat included pale or blotchy liver, pale kidneys, and

 haemorrhagic intestinal contents. No local skin irritation occurred.

 In the dog, a lethal intravenous dose of chlordimeform (50 mg/kg

 body weight) caused rapid and irreversible hypotension, and

 respiratory arrest followed cardiovascular collapse within a few

 seconds. Artificial respiration did not protect the animals against

 hypotension and death, suggesting cardiovascular collapse is probably

 the primary cause of death in dogs. Pathological examination following

 oral administration in dogs revealed congestion of liver, kidneys and

 lungs.

 The acute inhalation LC50 of chlordimeform base in rats

 (male and female) was 17 400 mg/m3 and for chlordimeform HCl was

 >5800 mg/m3 (FAO/WHO, 1972).

 The acute dermal toxicity data for metabolites of chlordimeform

 is presented in Table 7.

 Table 5. Acute toxicity of chlordimeform in experimental animals

 Species Sex Route LD50 References

 (mg/kg

 body weight)

 Rat male/female oral 250 FAO/WHO (1972)

 male/female oral 340 Worthing & Walker (1983)

 male/female oral 123 Robinson et al. (1975)

 male/female oral 301 Gaines & Linder (1986)

 male/female oral 178-220 FAO/WHO (1972)

 male/female oral 178 FAO/WHO (1972)

 female oral 170-460 FAO/WHO (1972)

 female oral 265 Gaines & Linder (1986)

 female oral 460 FAO/WHO (1972)

 male/female dermal 640 FAO/WHO (1972)

 male dermal 337 Gaines & Linder (1986)

 female dermal 263 Gaines & Linder (1986)

 Mouse male/female oral 290 Haddow & Shankland (1969)

 male oral 267 Ghali & Hollingworth (1985)

 male/female ip 110 FAO/WHO (1972)

 Rabbit - oral 625 FAO/WHO (1972)

 - oral 625 Worthing & Walker (1983)

 Dog male oral approx.150 Hurni & Sachsse (1969)

 female oral approx.100 Hurni & Sachsse (1969)

 Table 6. Acute toxicity of chlordimeform hydrochloride in

 experimental animals (FAO/WHO, 1972)

 Species Sex Route LD50

 (mg/kg body weight)

 Rat male oral 305

 male oral 325

 female oral 330

 male iv 95

 - dermal approx. 4000

 Mouse male/female oral 220

 Rabbit - dermal >4000

 Table 7. Acute toxicity of chlordimeform metabolites in the rat (FAO/WHO, 1972)

 Metabolite Sex Route LD50

 (mg/kg

 body weight)

 N-formyl-4-chloro-o-toluidine male/female oral 2900

 4-chloro-o-toluidine (base) male/female oral approx.1000

 4-chloro-o-toluidine-HCl male/female oral 860

 N-formyl-4-chloro-o-toluidine male/female dermal (24 h) >2150

 4-chloro-o-toluidine (base) male/female dermal (24 h) approx.1800

 4-chloro-o-toluidine-HCl male/female dermal (24 h) >2150

 7.2 Short-term exposure

 7.2.1 Dietary

 Dietary studies of 60 days duration have been conducted in the

 mouse and rat with each of chlordimeform, N-formyl-4-chloro -o-

 toluidine, and 4-chloro- o-toluidine.

 7.2.1.1 Mouse

 In a study with chlordimeform by Sachsse et al. (1979a), groups

 of Tif:MAGf mice (30/sex/group), housed under SPF conditions, were fed

 a diet containing chlordimeform at concentrations of 0, 750, 1500,

 3000 or 6000 mg/kg for 60 days. This corresponded to dietary intakes

 of 0, 107, 194, 717 or 1525 mg/kg body weight per day for females and

 0, 110, 200, 669 or 1519 mg/kg body weight per day for males. At the

 end of the 60-day period, all animals were examined for haematology,

 blood chemistry and urinalysis parameters, and groups of 10 male and

 10 female animals from the control and the lower three dose groups

 were subjected to gross and microscopic examination of tissues and

 organs. Mortality was observed in the two highest dose groups over the

 course of the study. The highest dose group was terminated after two

 weeks because of a poor general condition of the animals. Growth, as

 shown by body weight gain, was reduced in all dietary groups. Food

 consumption was reduced at all dietary levels in females only. No

 clinical signs of toxicity were noted. Ophthalmological and auditory

 examinations were normal. Haematological investigations showed

 haemolytic anaemia in both sexes of all treated groups, which was

 characterized as a reduction in haemoglobin concentration, red blood

 cell count, and packed cell volume. The anaemia was associated in a

 dose-related manner with an increased methaemoglobin concentration and

 an increase in Heinz body formation. At 3000 mg/kg diet, there was a

 slight reticulocytosis noted in both sexes. This was accompanied in

 females by a shift in the differential leucocyte count noted as an

 increase in the percentage of polymorphonuclear neutrophile and a

 decrease in the percentage of lymphocytes. Small changes were observed

 in alkaline phosphatase activity, which was slightly increased in male

 mice at the highest dose level. Total protein concentration was also

 slightly reduced in female mice at the highest dose level. Urinalysis

 was unremarkable. In the animals that died or were killed within the

 first 2-week period, all were found to be emaciated and in poor

 general condition. In all treated animals dying during the test

 period, congestion of the organs, especially of the liver, was

 observed. At the highest dose level, atrophy of thymic tissue was

 observed. There was an increased haemosiderosis at the two highest

 dose levels. There were no other pathological findings associated with

 the presence of chlordimeform in the diet.

 In a study with N-formyl-4-chloro- o-toluidine by Sachsse et

 al. (1980a), groups of Tif:MAGf mice (30/sex/group), housed under SPF

 conditions, were fed a diet containing N-formyl-4-chloro- o-

 toluidine at concentrations of 0, 750, 1500, 3000 or 6000 mg/kg for

 60 days. This corresponded to dietary intakes of 0, 138, 379, 1203,

 or 3153 mg/kg body weight per day for females and 0, 140, 349, 1023,

 2549 mg/kg body weight per day for males. At the end of the 60-day

 period, all animals were examined for haematology, clinical chemistry

 and urinalysis parameters. A group of 10 males and 10 females from

 each dose level was examined for gross and microscopic pathological

 changes at the conclusion of the study. Mortality was observed

 predominantly at the high-dose level over the course of the study.

 There were no clinical signs of toxicity, although food consumption

 and growth were depressed at 1500 mg/kg and above in both sexes over

 the course of the study. Ophthalmological and auditory examinations

 were unremarkable. Significant haematological abnormalities were

 observed at all dose levels at the conclusion of the study. Haemolytic

 anaemia was observed in both males and females and was characterized

 as a reduction in haemoglobin concentration, erythrocyte count

 and packed cell volume. There was a dose-related increase in

 methaemoglobin concentration and an increase in Heinz body formation.

 Additionally, both males and females in all treated groups showed a

 significant reticulocytosis, thrombocytaemia, and leucocytosis. At

 higher dose levels in both males and females, the leucocytosis was

 accompanied by a shift in the differential leucocyte count. There was

 a slight increase in the activity of SGOT, SGPT and SAP. Urinalysis

 revealed somewhat lower specific gravity and the presence of bile

 pigment in animals at the two highest dietary concentrations.

 Microscopic examination of tissues and organs revealed cytomegaly and

 hyperplasia of the bile duct epithelium and Kupffer cells in some

 animals at 750 mg/kg and in most animals at higher dose levels.

 Nuclear inclusion bodies were also evident in all treated animals and,

 at the highest dose level, moderate centrilobular fatty changes were

 observed. Additionally, at the higher dose levels, atrophy of thymic

 lymphoid tissue and of splenic white pulp was observed. Substantial

 hyperplasia of the epithelium of the urinary bladder was observed in

 most animals at the highest dose level and sporadically throughout the

 treated groups.

 In a study with 4-chloro- o-toluidine by Suter et al. (1976a),

 groups of mice (30/sex/group, TIF:NMRI strain) were bred and

 maintained under SPF conditions and fed a diet containing 4-chloro-

 o-toluidine at concentrations of 0, 750, 1500, 3000 and 6000 mg/kg

 for 60 days. Mortality of 50% was observed in the 6000 mg/kg group.

 There were no clinical signs of toxicity, although food intake and

 growth were retarded at the two highest dose levels. Eye examinations

 did not indicate adverse ocular changes. Haemolytic anaemia occurred

 in both sexes of all treated groups and was characterized by

 reticulocytosis and Heinz body formation. In the male mice of all

 treated groups, haemoglobin concentration, packed cell volume and

 erythrocyte counts were slightly below that of controls. In addition,

 leucocytosis was observed in all animals of all dosage groups with

 the exception of females at the 750 mg/kg level. In both sexes at

 6000 mg/kg and in the females at 3000 mg/kg total protein

 concentration was reduced and blood glucose and urea nitrogen values

 were increased. Plasma GPT was increased in male mice at 3000 mg/kg

 and above and in females at 1500 mg/kg. Microscopic examination of

 tissues and organs at the conclusion of the studies showed slight to

 moderate vacuolar changes in hepatocytes, which were pronounced in

 animals at the 3000 mg/kg level and above. There was also a marked

 congestion of the spleen at these high dose levels. In addition, the

 urinary bladder revealed hyperaemia and dilation of the capillaries in

 the mucosal layer. These changes were accompanied by oedema, multiple

 intra-epithelial haemorrhage and focal proliferation of the

 transitional cell epithelium. On occasion, these changes in the

 urinary bladder were noted at the lowest concentration.

 7.2.1.2 Rat

 In a study with chlordimeform by Sachsse et al. (1979b), groups

 of Tif:RAIf rats (20/sex/group) were fed a diet containing

 chlordimeform at concentrations of 0, 750, 1500, 3000 or 6000 mg/kg

 for 60 days. This corresponded to dietary intakes of 0, 84, 137, 222

 or 462 mg/kg body weight per day for males and 0, 71, 121, 231 or

 464 mg/kg body weight per day for females. Groups of 10 males and 10

 females were killed at 60 days and had complete haematology, clinical

 chemistry and urinalysis parameters examined. At the end of the study,

 10 males and 10 females from each group were subjected to gross and

 microscopic pathological examination. Animals that died during the

 course of the study were similarly examined. Food intake and growth

 were reduced over the course of the study at all dose levels. Slight

 mortality was observed at the highest concentration. There were no

 clinical signs of toxicity or adverse behaviour at any dose level.

 Slight changes in several haematological parameters were noted at the

 two highest levels. Methaemoglobin levels were increased in a dose-

 related manner at all treatment levels. Heinz bodies were noted in

 haematological examination at 1500 mg/kg and above. Slight changes

 were noted in several clinical chemistry para-meters including

 decreased glucose concentration, increased alkaline phosphatase

 activity and increased œ-glutamyl transpeptidase activity,

 predominantly at the three highest dose levels. Urinalyses showed

 slight changes at the two highest dose levels including a reduced

 urine volume, reduced protein concentration, and reduced electrolyte

 (potassium) level, predominantly at the highest dietary levels.

 Terminal body weights of all animals administered chlordimeform were

 significantly reduced in a dose-related fashion. Substantial changes

 in growth and relative organ weights were noted in both males and

 females at all dietary levels. Reductions in the weight of such organs

 as the brain, heart, liver, kidneys, adrenals and thymus were reported

 for both males and females. In males, reduced kidney and testes

 weights were noted only at the highest dose level while reduced

 ovarian weights were noted at all dose levels. Other than excessive

 emaciation at the highest dose level, no gross anatomical changes were

 noted in the animals killed for pathological examination. In most rats

 of the highest-dose groups, haemosiderosis in the spleen was observed.

 Reduced spermatogenesis was noted at the highest concentration. Focal

 hyperplasia of small biliary ducts and of the transitional epithelium,

 and increased vascularization in the mucous membrane of the bladder

 were observed in the highest-dose group. In addition, the highest-dose

 group showed thymic atrophy in several of the animals examined. No

 compound-related histopathological changes were noted in rats fed

 1500 mg/kg or below in the diet.

 In a study with N-formyl-4-chloro- o-toluidine by Sachsse et

 al. (1980b), groups of Tif:RAI rats (30/sex/group) were fed a diet

 containing N-formyl-4-chloro- o-toluidine at concentrations of 0,

 750, 1500, 3000 or 6000 mg/kg for 60 days. This corresponded to

 dietary intakes of 0, 91, 176, 347 or 875 mg/kg body weight per day

 for males and 0, 87, 165, 329 and 719 mg/kg body weight per day for

 females. Groups of 10 males and 10 females were killed at the

 conclusion of the study for complete haematological, clinical

 chemistry and urinalysis examinations, and gross and microscopic

 pathological examinations of tissues and organs. Extensive mortality

 was observed at the high-dose level within the first few weeks of the

 experiment. At the end of the third week of treatment, the highest-

 dose group was terminated. There was no substantial mortality at 3000

 or lower. Food intake and growth were reduced over the course of the

 study in a dose-dependent fashion in all dose groups. Apart from the

 mortality noted at the high dose level, no clinical signs of toxicity

 or adverse behaviour were observed. Auditory and ophthalmological

 examinations showed no evidence of loss of these functions in any of

 the animals examined. Haematological examination indicated haemolytic

 anaemia in both sexes of all treatment groups; characterized by a

 reduction in haemoglobin concentration, erythrocyte count and packed

 cell volume, and an increase in methaemoglobin level. Heinz bodies

 were observed at 3000 mg/kg only. In addition, at 1500 mg/kg and above

 there was a slight reticulocytosis and reduced partial thromboplastin

 time in these dose groups. Changes in the clinical chemistry

 parameters were noted at both 1500 and 3000 mg/kg. Gross examination

 of certain tissues and organs showed changes in absolute weights

 and relative weight ratios at all dosage levels. These reductions

 appeared to follow a dose-dependent relationship. Animals administered

 6000 mg/kg showed atrophy of the thymus and spleen within the first

 three weeks of the test. Liver changes were noted in all dose groups

 characterized as hyperplasia of the bile duct epithelium and changes

 in the distribution of lipid. At the highest dose level, hyperplasia

 of the urinary bladder epithelium and testes was noted. About half the

 animals of both sexes in the 6000 mg/kg group showed an increase in

 the mitotic index in hepatocytes.

 In a study of 4-chloro- o-toluidine by Suter et al. (1976b),

 groups of rats (30/sex/group; Tif/RAI strain) were fed a diet

 containing 4-chloro- o-toluidine at concentrations of 0, 750, 1500,

 3000 and 6000 mg/kg for 60 days. There was no mortality over the

 course of the study and clinical signs of toxicity were not observed.

 Ophthalmological examinations did not suggest changes related to the

 presence of 4-chloro- o-toluidine in the diet. Growth was reduced at

 dietary levels of 1500 mg/kg and above. Haemolytic anaemia in both

 sexes of all treated groups was characterized by a variety of

 haematological changes, including reduced haemoglobin content, reduced

 haematocrit content, reduced blood cell count, increased

 methaemoglobin content, Heinz body formation, reticulocytosis and

 polychromatophilia. In the highest-dose group, an increased number

 of immature red blood cells (normoblasts) were observed. An increased

 leucocyte count and prothrombin time was recorded at 3000 and

 6000 mg/kg. Total protein was slightly reduced at 3000 and 6000 mg/kg

 and there was a shift in the globulin content as observed by

 electrophoresis. Plasma œ-glutamyl transpeptidase of males and

 alkaline phosphatase of females was increased at 6000 mg/kg.

 Urinalysis was not significantly affected. In all treated animals, the

 liver showed an increase in size accompanied by hypertrophy of the

 hepatocytes. In the two highest-dose groups, the spleen was enlarged

 and microscopic examination showed pronounced congestion and

 haemorrhage. In the highest-dose group, slight or moderate

 proliferation of the transitional cell epithelium was noted in the

 urinary bladder.

 7.2.1.3 Dog

 In a study with chlordimeform by Blackmore (1969a), four groups

 of beagle dogs were fed a dry diet containing either 0 mg/kg (10/sex),

 250 mg/kg (8/sex), 500 mg/kg (8/sex) or 1000 mg/kg (10/sex) of

 chlordimeform for 2 years. Two male and two female dogs were

 sacrificed from each group at 26 and 52 weeks. Body weight was reduced

 at 1000 mg/kg, the effect being slightly more pronounced in the

 females. Total leucocyte counts were sporadically elevated in both

 sexes at 1000 mg/kg and in females at 500 mg/kg. Haematocrit,

 haemoglobin and erythrocyte counts tended to be depressed after 2

 years in both sexes at 1000 mg/kg. Sporadic slight decreases in serum

 albumin were observed, more frequently in males, at 1000 mg/kg.

 Terminal spleen-to-body weight ratio was elevated in males at 500 and

 1000 mg/kg, and in females at 1000 mg/kg. Histopathological

 examinations revealed bile duct hyperplasia, pericholangitis and

 nodular hepatocytic hyperplasia at 500 and 1000 mg/kg in both sexes,

 and nodular hepatocytic hypertrophy at 1000 mg/kg in both sexes in the

 liver. Kidneys showed an increased amount of pigmentation at 500 and

 1000 mg/kg in both sexes.

 7.2.2 Intubation

 7.2.2.1 Rat

 Four groups of 10 male and 10 female rats were intubated six

 times weekly for one month with 5 ml/kg body weight of a 2% solution

 of carboxymethylcellulose containing chlordimeform base at

 concentrations such as to give dose levels of 0, 25, 50 or 100 mg/kg

 (FAO/WHO, 1972). Body weight was markedly reduced in both sexes at

 100 mg/kg. Hyperexcitability was observed in all test animals. At

 100 mg/kg, this was apparent 20-30 min after dosing, and was followed

 2 to 3 h after dosing by decreased activity and apathy. Recovery was

 complete at 4 h. Similar but reduced effects were observed at 50 and

 25 mg/kg, and with inconsistent frequency.

 7.3 Long-term dietary exposure

 7.3.1 Mouse

 While there have been a number of long-term studies in mice with

 chlordimeform and its metabolites, these were specifically designed to

 study carcinogenic potential and are described in section 7.7.1.

 7.3.2 Rat

 In a study with chlordimeform by Blackmore (1969b), groups of

 rats (35/sex/group) were fed a diet containing 0, 100, 250, 500 or

 1000 mg/kg chlordimeform for 2 years. The 100 mg/kg group commenced

 treatment 7 weeks after the other groups. This group was originally

 part of the control group. Animals at that time were of similar weight

 to those that had already been on test. The 1000 mg/kg group was

 discontinued at 3 months due to severe growth inhibition. Growth

 inhibition was observed in the males at 500 and 1000 mg/kg. In the

 females, weight gain was reduced at 250 mg/kg and above. In addition,

 female body weight gain was reduced at 100 mg/kg between weeks 20 and

 48. Food intake was significantly reduced at 500 and 1000 mg/kg in

 both sexes. Dose-related decreases in haematocrit, haemoglobin, and

 erythrocyte counts, and a dose-related increase in the leucocyte count

 occurred in females at 250 and 500 mg/kg up to one year. During the

 second year, haematocrit only was consistently depressed in females at

 500 mg/kg. Histopathological changes in the liver (nodules, and foci

 of hyperplasia of hepatocytes) occurred in all groups, but the

 incidence was greater at 250 and 500 mg/kg and was more severe at

 500 mg/kg. Some females at 500 mg/kg showed slight hypertrophy and

 vacuolation of focal groups of cells in the adrenal cortex. Terminally

 organ to body weight ratios were increased in the liver (females at

 250 and 500 mg/kg and males at 100 and 250 mg/kg), kidney (females at

 250 and 500 mg/kg), thyroid (females at 250 and 500 mg/kg), heart

 (males at 250 mg/kg and females at 500 mg/kg), adrenals (males at 100

 and 250 mg/kg) and testes (100 and 500 mg/kg).

 In a study with chlordimeform by Zak et al. (1973), groups of

 rats (25/sex/group) were fed a diet containing chlordimeform at

 concentrations of 0, 50, 75, 100, 250 and 500 mg/kg for one year. Food

 consumption and weight gain data were recorded through the study.

 Terminal organ weights and gross and microscopic examinations of

 tissues and organs were the only other parameters reported. The

 500 mg/kg group was terminated at 37 weeks after 10 males and 8

 females had died. At the conclusion of the study, there was

 considerable mortality noted in all groups. Food consumption was

 decreased at 500 mg/kg in both sexes and was slightly reduced at

 100 mg/kg and above in males only. This reduced food consumption was

 not significantly reflected in the growth curves of males and females.

 Gross examination did not show any compound-related abnormalities.

 Organ weights and organ/body weight or organ/brain weight ratios did

 not differ from control values. Histological examinations of liver and

 spleen were performed on all animals. There were no significant

 differences from control values with respect to fatty changes and

 inflammatory changes in the liver. Slight proliferation of the bile

 duct was more frequent in female rats treated with 500 mg/kg than in

 the rats of other treated groups or the control group. Results of

 examinations of the spleen for haemosiderosis suggested that, while

 this condition was more pronounced in females, there were no

 significant differences from control values.

 In a study by Sachsse et al. (1980c), rats (90/sex/group;

 Tif: RAIf strain) were fed a diet containing chlordimeform at

 concentrations of 0, 2, 20, 100 or 500 mg/kg for 24 months. This was

 equivalent to dosage levels of 0, 0.1, 1.0, 5.0 and 24 mg/kg body

 weight per day for males and 0, 0.1, 1.2, 6.0, and 28 mg/kg body

 weight per day for females. At the conclusion of the dietary feeding

 study, all remaining rats were fed control diets for a period of time

 until a survival rate of 20% per sex (10 rats) per group was attained,

 at which time the animals were killed and examined. Groups of 20 male

 and 20 female rats per group were examined periodically (4, 13, 26,

 52, 78 and 104 weeks) for clinical laboratory investigations including

 haematology, blood chemistry and urinalysis. Groups of 10 animals/sex/

 group were sacrificed at 27 and 52 weeks for gross and microscopic

 examination of tissues and organs. At the conclusion of the study, all

 animals sacrificed (also those that died prior to the termination)

 were examined for gross and microscopic pathology. There was no

 mortality in the study attributable to the presence of chlordimeform.

 Growth and body weight were maintained in all groups with the

 exception of the 500 mg/kg group, where growth in both sexes was

 slightly retarded. There were no clinical signs of toxicity or

 abnormal behaviour. Ophthalmological and auditory examinations,

 performed at periodic intervals, revealed no adverse effects

 attributable to chlordimeform. Methaemoglobinaemia was observed at

 dose levels of 20 mg/kg diet and above. At week 4, both males and

 females showed a slight, but statistically significant, increase in

 methaemoglobin content. At weeks 13 and 26, this condition abated but

 returned at the end of one year and was significant in both sexes at

 the highest dose level for the remainder of the study. Changes in

 several other blood chemistry parameters were observed at the highest

 dose level. Heinz body formation generally associated with

 methaemoglobinaemia was not observed at week 4, but at the end of year

 one and thereafter Heinz bodies were observed at the highest dose

 level. A slight but significant reduction in blood glucose

 concentration was noted at the higher dose levels throughout a major

 part of the study. Slight changes in urinalysis parameters were

 observed in the highest dose group, including a slightly reduced

 urinary volume and a slightly higher specific gravity. Ketonuria and

 proteinuria were observed at the high dose level at the earliest

 examination periods only and were not observed at 13 weeks and

 thereafter. Gross pathology and organ weight measurements (provided

 for 27, 52 and 106-week sacrifice intervals) did not show any

 significant dose-related responses. Microscopic histopathological

 analyses of tissues and organs (performed at weeks 27 and 52 and at

 the termination of the study) indicated no significant changes

 attributable to chlordimeform in the diet. Although numerous benign

 and malignant tumours were observed in both treated and control

 animals, the frequency and type of neoplasms, reported at 12 and 24

 months with pathology analyses, were not dose-related nor were they

 attributable to chlordimeform in the diet. Several inherent,

 degenerative or inflammatory changes were attributed to disease,

 common in older animals. There was no indication of carcinogenic

 potential to rats as a result of the presence of chlordimeform in the

 diet. Based on the haematological occurrence of methaemoglobinaemia,

 the no-observed-effect level of chlordimeform for rats was 2 mg/kg

 diet, corresponding to an intake of 0.1 mg/kg body weight per day.

 In a study with N-formyl-4-chloro- o-toluidine by Sachsse et

 al. (1980d), groups of Tif:RAIf rats (90/sex/group) were fed a diet

 containing N-formyl-4-chloro- o-toluidine at concentrations of

 0, 2, 20, 100, or 500 mg/kg for 2 years. This corresponded to dietary

 intakes of 0, 0.1, 1.0, 5 or 30 mg/kg body weight per day for females

 and 0, 0.1, 1.0, 4.0 or 24 mg/kg body weight per day for males. Groups

 of 10 males and 10 females were killed at periodic intervals (26 and

 52 weeks) for examination of gross and microscopic pathology. Complete

 haemato-logical, clinical chemistry, and urinalysis examinations were

 performed at 4, 13, 26, 52 and 78 weeks on 20 males and 20 females of

 each group. At 24 months, 20 males and 20 females were killed and

 examined for clinical laboratory parameters and gross pathology. The

 remaining animals were fed control diets for additional periods of

 time until a survival rate of 20% per sex per group was attained.

 At that time the remaining animals were killed and examined

 microscopically for patho-logical changes, especially neoplastic and

 non-neoplastic lesions. In the high-dose group, food intake and growth

 were affected over the course of the study and slight growth

 retardation was observed. Clinical signs of toxicity or adverse

 behaviour were not observed. There was no mortality in the study

 attributable to the presence of N-formyl-4-chloro- o-toluidine.

 Ophthalmological examinations and auditory tests were normal. The

 results of the haematological investigation showed haemoglobin

 concentration to be slightly, but significantly, below that of the

 controls in both male and female rats at the two highest dose levels.

 In addition, slight but significant decreases in the erythrocyte count

 and packed cell volume, a slight increase in reticulocytes and

 somewhat higher methaemoglobin values were also seen in both male and

 female rats at 500 mg/kg. With the exception of lower body weights of

 the animals at the highest concentration, the most obvious change was

 a significant increase in absolute and relative liver weights in both

 sexes, but more pronounced in females, in the 500 mg/kg group. A

 significantly increased incidence of hyperplasia of small biliary

 ducts was seen in the liver of rats of the 500 mg/kg dose group. In

 rats of the 500 mg/kg group that were killed after 2 years or died

 after 12 months, a marked increase in the frequency of multioculated

 cholangiogenic biliary cysts in the liver was noted. Both of these

 finding were more pronounced and more frequent in female than in male

 animals. Numerous benign and malignant tumours were observed in both

 control and treated rats, but the frequency and types of neoplasms was

 not treatment-related. All gross and histopathological lesions and

 changes seen in both control and test animals were described as

 inherent, degenerative or inflammatory in origin and were attributed

 to naturally occurring diseases common in aged rats. There was no

 indication of oncogenic potential in rats as a result of the presence

 of N-formyl-4-chloro- o-toluidine. On the basis of the minor

 haematological changes, the no-observed-effect level in this study was

 20 mg/kg diet, corresponding to an intake of 1 mg/kg body weight per

 day.

 In a study with 4-chloro- o-toluidine by Sachsse et al. (1980e),

 groups of Tif:RAIf rats (90/sex/dose level) were fed a diet containing

 4-chloro- o-toluidine at concentrations of 0, 2, 20, 100 or 500 mg/kg

 for two years. This corresponded to dietary levels of 0, 0.1, 1.0, 5.0

 or 28 mg/kg body weight per day for females, and 0, 0.1, 1.0, 4.6 or

 24.6 mg/kg body weight per day for males. Groups of 10 males and 10

 females were killed at periodic intervals (27 and 54 weeks) for gross

 and microscopic pathological examinations. Complete haematological,

 clinical chemistry and urinalysis examinations were performed at 4,

 13, 26, 52, and 78 weeks on 20 females and 20 males of each group. At

 24 months, 20 males and 20 females were killed and examined for

 clinical laboratory parameters. Several animals were examined for

 gross pathology. The remaining animals were fed control diets for

 additional periods of time until a survival rate of 20% per group was

 attained. At that time, the remaining animals were killed and examined

 for microscopic pathology and oncogenic response. A complete

 microscopic analysis was made on at least 10 rats of each sex of each

 group at the termination of the experiment. All rats dying during the

 course of the study were examined for tumours or neoplasms. In the

 high-dose group of female rats, food intake and growth were affected

 over the course of the study and slight growth retardation was

 observed. There was no effect on growth in male rats at any dose

 level. Clinical signs of toxicity were not observed. There was no

 mortality in the study attributable to the presence of 4-chloro- o-

 toluidine in the diet. Ophthalmological examinations and auditory

 tests did not reveal changes that were related to the administration

 of 4-chloro- o-toluidine. The results of the haematological

 investigation, blood chemistry data and the urinalysis were similar

 for both treated and control rats. Periodically, the haemoglobin

 concentration was slightly but significantly below that of the

 controls in the female rats at 100 mg/kg diet and above. Slight but

 significant decreases were observed in the erythrocyte count and

 packed cell volume in the female rats at 500 mg/kg. Marginal

 reticulocytosis was also found to occur at 500 mg/kg in the female

 rats at week 13 and in both sexes at week 26. In both male and female

 rats at 500 mg/kg, the methaemoglobin level was found to be slightly

 though significantly increased when compared to controls.

 Periodically, this change was observed in the females of the 100 mg/kg

 dose group, and, occasionally, Heinz bodies were also observed in

 female rats. There were some changes to organ weights, organ-to-body

 weight ratios and organ-to-brain ratios that were statistically

 significant, but only the increase in absolute and relative liver

 weights were dose-related. In rats from the 500 mg/kg dose group only,

 a slightly but significantly increased incidence of multilobular

 cholangiogenic cysts was observed in the liver. These biliary cysts

 were found in 10/89 female and 3/90 male rats from the 500 mg/kg

 group, compared to 4/89 female and 0/90 male rats in the control

 group. Numerous benign and malignant tumours were observed in both

 control and treated rats, but the frequency and types of the neoplasms

 occurring in these animals was not treatment-related. Gross and

 histopathological lesions and changes seen in both control and treated

 animals were described as inherent, degenerative or inflammatory in

 origin, and were attributed to naturally occurring diseases, common in

 aged rats. There was no indication of oncogenic potential in rats as a

 result of the presence of 4-chloro- o-toluidine in the diet. On the

 basis of minor haematological changes, the no-observed-effect level in

 this study was 20 mg/kg diet, corresponding to a dietary intake of

 1 mg/kg body weight per day.

 7.4 Skin and eye irritation; skin sensitization

 Potential skin irritation was assessed by the application of

 0.5 g chlordimeform or its hydrochloride salt to the shaved skin of

 six male rabbits. When evaluated at 24 and 72 h, both compounds

 produced a very slight irritation (FAO/WHO, 1972).

 Potential eye irritation was assessed by application of 0.1 ml of

 chlordimeform to one eye of each of nine rabbits, followed by

 assessment over 7 days. All animals exhibited slight conjunctival

 redness, while one showed slight chemosis. All effects had reversed

 within 7 days. There was no evidence of corneal damage. Chlordimeform

 may be considered a slight eye irritant (FAO/WHO, 1972).

 There were no studies performed to assess the potential for

 chlordimeform to cause skin sensitization.

 7.5 Reproductive toxicity, embryotoxicity and teratogenicity

 7.5.1 Reproductive toxicity

 7.5.1.1 Rat

 Four groups of 10 male and 20 female rats were fed a diet

 containing 0, 100, 250 and 500 mg/kg chlordimeform in corn oil during

 three parental and three two-litter filial generations. Parental body

 weight prior to mating tended to be reduced in all treatment groups,

 especially at the highest dose level. The same tendency was apparent

 with regard to food consumption. The fertility index, gestation index,

 live birth index, sex ratio, mean litter size and birth weight of pups

 were comparable between treatment and control groups in all

 generations. At the 500 mg/kg dose level, the lactation index was

 reduced in Fla, Flb and F3a litters. Weaning weight of offspring was

 depressed in all high-dose litters. Gross pathological examinations

 were performed on parents and pups dying during the study, and on 10

 male and 10 female weanlings of the F3b generation. No compound-

 related effects were noted in the pathological examination (Blackmore,

 1969c).

 In a study by Goldman et al. (1991), treatment of ovariectomized

 Long-Evans rats with a single intraperitoneal injection of

 chlordimeform at dose levels of 25 or 50 mg/kg caused a complete

 suppression of luteinizing hormone surge. The observed suppression did

 not persist beyond the day of treatment. In a more recent study by

 Cooper et al. (1994), the effect of this delay in hormone surge on

 pregnancy outcome in females was examined. Chlordimeform at a dose

 level of 50 mg/kg resulted in a delay in breeding as well as a

 significant reduction in litter size.

 Adult male Sprague-Dawley rats were administered chlordimeform by

 gavage at 200 mg/kg body weight on one day or 50 mg/kg body weight per

 day for 5 days. Rats were killed on either 3 or 13 days after the last

 dose. Body weights were reduced at the earlier time points only. There

 were no changes in the weights of the testes or associated organs.

 Caudal sperm counts were reduced after the single dose only. No other

 changes were observed, including sperm motility, velocity or

 morphology (Linder et al., 1992).

 7.5.1.2 Hamster

 Goldman et al. (1993) reported that a single intraperitoneal dose

 of chlordimeform (75 mg/kg and above) is capable of delaying the

 luteinizing hormone surge and altering the timing of oocyte release in

 the hamster. The reproduction consequences of this effect were not

 investigated.

 7.5.2 Embryotoxicity and teratology

 7.5.2.1 Rat

 Groups of pregnant rats (25/treatment group, 30 controls) were

 administered chlordimeform in carboxymethylcellulose at dose levels of

 0, 10, 25 or 50 mg/kg body weight per day from days 6 to 15 of

 pregnancy. Only a slight reduction in feed intake was noted at the

 intermediate dose level. At the high dose level, dams showed

 somnolence through the first 3 days of treatment. There was also a

 reduced body weight gain and decrease in feed consumption at this dose

 level. Examination of fetuses removed by caesarean section on day 21

 showed there was a slight delay in growth of the fetuses at the two

 highest dose levels. This effect was probably a direct result of the

 toxic response in the dams. No teratogenic events were observed in the

 offspring, although an increased incidence of sternal ossification

 defects occurred at 25 mg/kg body weight (Fritz, 1975).

 7.5.2.2 Rabbit

 Three groups of 10 impregnated female New Zealand white rabbits

 were administered chlordimeform by gavage on days 8 to 16 of gestation

 at dose levels of 0, 7.5 or 30 mg/kg body weight per day. Five rabbits

 per group were killed on day 28 of gestation. Parental mortality,

 abortion rate, corpora lutea to implantation ratio, litter size,

 incidence of resorption, stillbirths, fetal weight, fetal length, and

 incidence of skeletal and tissue abnormalities were unaffected by the

 test compound. In the remaining rabbits, which were allowed to litter

 normally, gestation length, litter size and litter weights were

 similar in both treated and control groups (Blackmore, 1969d).

 Groups of rabbits (group size ranged from 17 to 38 dams per

 group) were given chlordimeform orally from days 6 to 18 of pregnancy

 at dose levels of 0, 10, 30 and 100 mg/kg body weight per day. Fetuses

 were removed by caesarean section on day 28 of pregnancy. The

 administration of chlordimeform at 100 mg/kg body weight produced a

 distinct adverse effect on dams for 2-3 h for the first 4 days of

 treatment. Examination of dams and fetuses at 28 days suggested that

 the low dose had no teratogenic or embryotoxic effect. In the

 intermediate and high dose groups, the implantation to corpora lutea

 ratio was found to be reduced compared to controls. In the high dose

 group, the number of incompletely ossified sternebrae showed a slight

 increase over that observed in the controls and in the other groups.

 In addition, the number of fetuses with malformations was slightly

 increased at 100 mg/kg. These malformations included a median cleft

 palate and exencephaly and an omphalocele. Further examination of

 spontaneous malformations observed in a cumulative control of 2495

 rabbit fetuses suggested that these abnormalities may be spontaneous

 and not a consequence of the administration of chlordimeform (Fritz,

 1971).

 7.6 Mutagenicity and related endpoints

 Referenced summaries of the test results with chlordimeform,

 N-formyl-4-chloro- o-toluidine, and 4-chloro- o-toluidine are

 given in Tables 8, 9 and 10, respectively. The important features of

 these data are given below.

 7.6.1 DNA damage and repair

 Chlordimeform gave no evidence of unscheduled DNA synthesis in

 rat hepatocytes (dose levels: 5-625 µg/ml) or in human fibroblasts

 (dose levels: 2-250 µg/ml). 4-Chloro- o-toluidine, on the other hand,

 gave a slight to moderate dose-related increase in the mean number of

 silver grains per nucleus in rat hepatocytes over a dose range of

 0.625-78.15 µg/ml, but not in human fibroblasts over the dose range of

 1.25-156.25 µg/ml.

 Table 8. Summary of mutagenicity and related end-point studies on chlordimeform HC1

 Organism Test Test system Strain +/- References

 Microorganisms Point mutation Salmonella typhimurium TA98 +/-S9 - Arni & Müller (1976a);

 TA100 +/-S9 - Konopka & Heymann (1977);

 TA1535 +/-S9 - Muecke et al. (1979);

 TA1537 +/-S9 - Rashid et al. (1984)

 TA1538 +/-S9 -

 Salmonella typhimurium TA98 - Arni & Müller (1983a)

 Intrasanguine host- TA100 -

 mediated assay TA1535 -

 Saccharomyces cerevisiae D7 +/-S9 - Arni & Müller (1983c)

 Escherichia coli WP2 +/-S9 - Rashid et al. (1984)

 WP2uvrA +/-S9 -

 WP67 +/-S9 -

 CM611 +/-S9 -

 CM571 +/-S9 -

 Insects Sex-linked recessive lethals Drosophila +a,b Kale et al. (1995)

 Mammalian cells Gene mutation Mouse lymphoma L5178Y- TK+/-/ - Beilstein & Müller (1984a)

 in vitro +/-S9

 Unscheduled DNA synthesis Rat hepatocytes - Puri & Müller (1983a)

 Unscheduled DNA synthesis Human fibroblasts - Puri & Müller (1983c)

 Mammalian cells Cell transformation Mouse BALB/3T3 cells +a,b Beilstein & Müller (1983)

 in vitro

 Table 8. (con't)

 Organism Test Test system Strain +/- References

 Mammals Testicular cell chromosome Mouse spermatocytes - Hool et al. (1983)

 damage Mouse spermatocytes - Arni et al. (1983a)

 Micronucleus assay Chinese Hamster bone - Langauer & Müller (1977)

 marrow interphase cells

 Chromosome aberrations Chinese hamster bone - Hool & Müller (1978)

 marrow metaphase cells

 Sister chromatid exchange Chinese hamster bone - Hool & Arni (1983a)

 marrow cells

 Heritable translocation Mouse - Lang & Adler (1982)

 Mammalian spot test Mouse - Lang (1984)

 Dominant lethal Mouse - Fritz (1978a)

 a Chlordimeform formulation

 b Not dose-related

 Table 9. Summary of mutagenicity and related end-point studies on N-formyl-4-chloro-o-toluidine

 Organism Test Test Systems Strain +/- References

 Microorganisms Point mutation Salmonella typhimurium TA98 +/-S9 - Arni & Müller (1976c);

 TA100 +S9 + Konopka & Heymann (1977);

 TA100 -S9 - Muecke et al. (1979);

 TA1535 +/-S9 - Rashid et al. (1984)

 TA1537 +/-S9 -

 TA1538 +/-S9 -

 Escherichia coli WP2 +/-S9 - Rashid et al. (1984)

 WP2uvrA +/-S9 -

 Wp67 +/-S9 -

 CM611 +/-S9 -

 CM571 +/-S9 -

 Mammalian cells in Gene mutation Mouse lymphoma L5178Y +a Strasser & Müller (1984b)

 vitro

 Mouse lymphoma L5178Y / -a Strasser & Müller (1983b)

 host-mediated assay

 Mammals Testicular cell chromosome Mouse spermatogonia - Arni (1983b)

 damage Mouse spermatocytes +b Arni & Müller (1983e)

 Micronucleus assay Chinese hamster bone - Langauer & Müller (1978a)

 marrow interphase cells

 Chromosome aberrations Chinese hamster bone - Hool & Arni (1983f)

 marrow metaphase cells

 Table 9. (con't)

 Organism Test Test Systems Strain +/- References

 Mammals Heritable translocation Mouse - Lang & Adler (1982)

 Mammalian spot test Mouse - Lang (1984)

 Dominant lethal Mouse - Fritz et al. (1978b)

 a No positive control

 b Chromosome aberrations; not dose-related

 Table 10. Summary of mutagenicity and related end-point studies on 4-chloro-o-toluidine

 Organisms Test Test system Strain +/- References

 Microorganisms Point mutation Salmonella typhimurium TA98 +S9 + Arni & Müller (1976b);

 TA98 +S9 - Haworth et al. (1983);

 TA98 -S9 + Konopka & Heymann (1977);

 Haworth et al. (1983);

 TA100 +S9 - Meuke et al. (1979);

 TA100 +S9 - Haworth et al. (1983)

 TA100 -S9 - Rashid et al. (1984);

 TA1535 +/-S9 - Haworth et al. (1983)

 TA1537 +/-S9 -

 TA1538 +/-S9 -

 S. typhimurium TA98 - Arni & Müller (1983b)

 Intrasanguine host- TA100 -

 mediated assay TA1535 -

 Saccharomyces cerevisiae D7 +/-S9 - Arni & Müller (1983d)

 Escherichia coli WP2 +/-S9 - Rashid et al. (1984)

 WP2uvrA +/-S9 -

 Wp67 +/-S9 -

 CM611 +/-S9 -

 CM571 +/-S9 -

 Mammalian cells in Gene mutation Mouse lymphoma L5178Y/TK+/- -S9 - Beilstein & Müller (1984b)

 vitro +S9 +

 Mouse lymphoma L5178Y + Strasser & Müller (1984a)

 Mouse lymphoma L5178Y - Strasser & Müller (1983a)

 /host-mediated

 Table 10. (con't)

 Organisms Test Test system Strain +/- References

 Mammalian cells in Unscheduled DNA synthesis Rat hepatocytes + Puri & Müller (1983b)

 vitro

 Human fibroblasts - Puri & Müller (1983d)

 DNA strand breakage V79 cells + Zimmer et al. (1980)

 Cell transformation Mouse BALB/3T3 cells + Beilstein & Müller (1984c)

 Mammals Testicular cell chromosome Mouse spermatogonia - Hool & Arni (1983b)

 damage Mouse spermatocytes - Hool & Arni (1983c)

 Micronucleus assay Chinese hamster bone - Langauer & Müller (1978b)

 marrow interphase cells

 Chromosome aberrations Chinese hamster bone - Hool & Arni (1983d)

 marrow metaphase cells

 Sister chromatid exchange Chinese hamster bone - Hool & Arni (1983e)

 marrow

 Sister chromatid exchange Chinese hamster ovary + Galloway et al. (1987)

 cells

 Heritable translocation Mouse - Lang & Adler (1982)

 Mammalian spot test Mouse + Lang (1984)

 Dominant lethal Mouse - Fritz et al. (1978)

 N-Formyl-4-chloro- o-toluidine was not directly tested for its

 ability to induce DNA damage and repair.

 The macromolecular binding of 4-chloro- o-toluidine to macro-

 molecules of rat and mouse liver has been investigated by several

 authors. In a report by Hill et al. (1979), the binding of

 4-chloro-2-[methyl-14C]-methylaniline (4-chloro- o-toluidine)

 in vivo and in vitro was investigated. The major binding

 in vivo was in the liver. In vitro binding was dependent on

 the presence for microsomal preparations and NADPH. Two soluble

 products of microsomal enzymes were identified as 5-chloro-2-

 hydroxylaminotoluene and 4,4'-dichloro-2,2'-dimethylazobenzene. The

 hydroxylamino compound appeared to be the more activated form of

 4-chloro- o-toluidine.

 4-Chloro- o-toluidine caused DNA strand breaks in Chinese

 hamster V79 cells (Zimmer et al., 1980).

 In studies by Bentley et al. (1986a,b), the covalent binding

 of [14C- ring]-4-chloro- o-toluidine to mouse and rat liver

 macromolecules was compared. After a single administration to either

 species, the extent of binding decreased in the order: protein>RNA>

 DNA. The level of binding to mouse liver DNA was approximately twice

 as high as the binding to rat liver DNA after either single or

 repeated administration, while the binding to liver RNA and protein

 was greater in the rat. There was no evidence of an increased level

 of incorporation of [3H]-thymidine into DNA as a result of

 4-chloro- o-toluidine binding. Two major hydrophobic DNA adducts

 were formed in both species, and one of these was formed to a much

 greater extent (6-30 fold) in mice.

 7.6.2 Mutation

 The ability of chlordimeform and its metabolites to induce

 mutations has been investigated in both microbial and mammalian

 systems.

 Chlordimeform itself gave uniformly negative results in

 Salmonella typhimurium (0.1-2000 mg/ml), Saccharomyces cerevisiae

 (15-400 mg/ml), and Escherichia coli (250-2000 mg/ml), with or

 without S9 microsomal activation, as well as in a thymidine kinase

 mutation assay in mouse lymphoma L5178Y/TK+/- cells with

 (75-3000 mg/ml) or without microsomal activation (42.5-1700 mg/ml).

 Kale et al. (1995) reported that a chlordimeform formulation diluted

 to provide a dose level of 10 000 µg/ml is a potent sex-linked

 recessive mutagen in male pre-meiotic and meiotic cells of Drosophila.

 N-Formyl-4-chloro- o-toluidine was also negative in all

 Salmonella typhimurium assays (0.1-1000 µg/ml) except for TA100 with

 microsomal activation, in which there was a dose-related increase in

 revertants. All Escherichia coli assays (250-2000 µg/ml) were

 negative. In a forward mutation assay in mouse lymphoma L5178Y cells

 (213 & 640 µg/ml), N-formyl-4-chloro- o-toluidine gave a positive

 result in two out of three 18-h incubation experiments. In a host-

 mediated experiment with mouse lymphoma L5178Y cells (300 mg/kg), the

 result was negative.

 4-Chloro- o-toluidine was negative in all assays with

 Salmonella typhimurium (10-2000 µg/ml) except for TA100 with S9

 microsomal activation and TA98 with S9 microsomal activation. Assays

 with Saccharomyces cerevisiae (3.2-90 µg/ml) and with Escherichia

 coli (250-2000 µg/ml) were negative. In a thymidine kinase forward

 mutation assay in mouse lymphoma L5178Y/TK+/- cells, 4-chloro- o-

 toluidine was negative without S9 microsomal activation (31.25-

 500 µg/ml) and positive with microsomal activation (37.5-600 µg/ml).

 In a separate forward mutation assay in mouse lymphoma L5178Y cells

 (111 & 255 µg/ml), a positive result was obtained in one out of three

 18-h incubation experiments. In a host-mediated experiment with mouse

 lymphoma L5178Y cells (330 mg/kg), the result was negative.

 7.6.3 Chromosome damage

 Sister chromatid exchange assays in Chinese hamster bone marrow

 cells were conducted following oral treatment with chlordimeform

 (31-324 mg/kg) and 4-chloro- o-toluidine (100-400 mg/kg). In both

 cases, the result was negative. Similarly, in an assay for chromosome

 aberrations in Chinese hamster bone marrow metaphase cells, a negative

 result was obtained following oral treatment with chlordimeform

 (2 × 60-240 mg/kg), N-formyl-4-chloro- o-toluidine (2 × 300-

 1200 mg/kg) and 4-chloro- o-toluidine (2 × 100-800 mg/kg), although

 the results were somewhat erratic. A micronucleus test in Chinese

 hamster bone marrow interphase cells following oral treatment with

 chlordimeform (2 × 60-240 mg/kg), N-formyl-4-chloro- o-toluidine

 (2 × 300-1200 mg/kg) and 4-chloro- o-toluidine (2 × 100-400 mg/kg)

 was also negative.

 Testicular cell chromosomal damage was assessed in mouse

 spermatocytes and spermatogonia. To investigate the potential

 cytogenetic effects on mouse spermatogonia, chlordimeform

 (9-66 mg/kg), N-formyl-4-chloro- o-toluidine (80-320 mg/kg) or

 4-chloro- o-toluidine (85-500 mg/kg) was administered orally on 5

 consecutive days. The results were negative in each case. To

 investigate the potential cytogenetic effects on mouse spermatocytes,

 chlordimeform (18-72 mg/kg), N-formyl-4-chloro- o-toluidine

 (80-320 mg/kg), or 4-chloro- o-toluidine (85-500 mg/kg) was

 administered orally over 10 days on days 0, 2, 3, 5 and 9. The results

 were negative in the case of both chlordimeform and 4-chloro- o-

 toluidine, but non-dose-related evidence of chromosome damage was

 indicated from the results with N-formyl-4-chloro- o-toluidine.

 The heritable translocation assay, dominant lethal test, and

 mammalian spot test, each of which might indicate minor or major

 genomic changes, were conducted on all three compounds. In the

 heritable translocation assay, chlordimeform (120 mg/kg/day),

 N-formyl-4-chloro- o-toluidine (100 mg/kg/day) or 4-chloro- o-

 toluidine (200 mg/kg/day) was administered orally for 49 days. No

 induction of translocation heterozygosity was found.

 In the dominant lethal assay, chlordimeform (22 or 66 mg/kg),

 N-formyl-4-chloro- o-toluidine (105 or 315 mg/kg) or 4-chloro- o-

 toluidine (110 or 330 mg/kg) was administered orally as a single dose.

 There was no evidence of any dominant lethal effects in the progeny of

 male mice.

 In the mammalian spot test, chlordimeform (160 mg/kg),

 N-formyl-4-chloro- o-toluidine (100 mg/kg) or 4-chloro- o-

 toluidine (100 mg/kg) was administered orally on days 8-10 of

 embryonic development. The results were negative except in the case of

 4-chloro- o-toluidine, which induced a 3.2% incidence of spots of

 genetic relevance compared to an incidence of 0.9% in controls.

 7.6.4 Cell transformation

 Cell transformation assays conducted with both chlordimeform and

 4-chloro-toluidine in mouse BALB/3T3 cells produced an increased

 incidence of transformed cell colonies with both compounds. With

 chlordimeform, the experiment was conducted at dose levels up to

 1 µg/ml, and increased transformation frequency was observed only at

 0.0625 and 0.125 µg/ml. The transformative properties of chlordimeform

 were considered weak. With 4-chloro- o-toluidine, three experiments

 were conducted at dose levels up to 36 µg/ml, and a significant

 increase in transformation frequency was observed. The transformative

 properties of 4-chloro- o-toluidine were considered definite.

 7.7 Carcinogenicity

 A number of carcinogenicity studies have been conducted in mice.

 With chlordimeform, there are two dietary studies and one dermal

 study. With N-formyl-4-chloro- o-toluidine, there is one dietary

 study. With 4-chloro- o-toluidine, there are four dietary studies.

 In rats, the carcinogenic potential of chlordimeform and its

 metabolites was generally investigated as part of more detailed

 long-term studies, and details are provided in section 7.3.1.2. Three

 studies on 4-chloro- o-toluidine that primarily investigated

 carcinogenicity are reported below.

 7.7.1 Mouse

 The carcinogenicity of chlordimeform has been examined in two

 dietary studies and in one dermal study.

 In a study by Suter et al. (1978), groups of mice (50/sex/group;

 Tif: MAG strain, SPF derived) were fed a diet containing chlordimeform

 at concentrations of 0, 20, 100 and 500 mg/kg for 24 months. At the

 conclusion of the dietary feeding interval, animals were maintained on

 control diet until 90% of a group had died, at which time the

 remaining animals of the group were sacrificed. There were no signs of

 acute toxicity related to chlordimeform in the diet over the course of

 the feeding trial. Growth and food consumption were similarly

 unaffected by the presence of chlordimeform in the diet. Mortality was

 significantly increased in females after 60 weeks at 500 mg/kg, and

 after 90 weeks at both 100 and 500 mg/kg. In males, significantly

 increased mortality was observed after 70 weeks at 500 mg/kg, and

 after 110 weeks at both 100 and 500 mg/kg. However, lifespan was not

 significantly affected in males at 100 mg/kg. The animals fed dietary

 levels of 100 mg/kg and above displayed an increased incidence of

 haemorrhagic tissue masses in subcutaneous tissues, retroperitoneum

 and some internal organs (kidney, liver and spleen), which upon

 examination were classified as malignant haemangioendotheliomas. These

 malignancies which were reported to occur rarely in control

 populations were found predominantly in the 100 and 500 mg/kg dietary

 groups (see Table 11). In some animals the tumours were of multiple

 origin and metastases were observed in the lungs. There were no other

 types of neoplasm observed in the study that were attributable to

 chlordimeform in the diet. Under the conditions of this study,

 20 mg/kg in the diet appeared to be a no-observed-effect level.

 In a study by Li et al. (1985a), groups of Swiss mice (50/group,

 sex not stated) were fed a diet containing chlordimeform at

 concentrations of 0, 20, 100, or 300 mg/kg for a period of 18 months.

 A positive control group was administered 300 mg/kg of 4-chloro- o-

 toluidine in the diet for 18 months. All animals were killed at the

 end of the study and assessed for tumour formation. The main results

 of the study are presented in Table 12. The author described the

 majority of the neoplasms as angiomas, and the malignant neoplasms as

 angiosarcomas. These neoplastic changes were considered to be similar

 to those observed in the study by Suter et al. (1978).

 In a paper by Jiang et al. (1988), the dermal carcinogenicity of

 chlordimeform was investigated in mice. Groups of Swiss mice (50 per

 dose level, sex not stated) were treated dermally with chlordimeform

 twice per week at dose levels of 0, 100, 500, 2000 or 4000 mg/kg body

 weight for a total of 17-20 treatments, together with croton oil (0.5%

 in acetone). Positive controls received coal tar pitch (20 treatments)

 plus croton oil (30 treatments). All animals were sacrificed after 18

 months and analysed for tumour formation. Chlordimeform induced both

 skin and liver tumours in this assay (see Table 13). The changes

 observed in the skin consisted of epidermal hyperplasia, papillomas

 and squamous cell carcinomas. The effect of croton oil application was

 Table 11. Incidence of haemangioendotheliomas in mice following dietary administration

 of chlordimeform, N-formyl-4-chloro-o-toluidine or 4-chloro-o-toluidine

 (Suter et al., 1978; Sachsse et al., 1978a,b)

 Control Dietary concentration (mg/kg)

 2 20 100 500

 **Chlordimeform HCl**

 Male 1/44 (2%) - 0/44 (0%) 15/49 (30%) 39/48 (83%)

 Female 1/43 (2%) - 2/46 (4%) 22/46 (50%) 35/49 (71%)

 Total 2/87 (2%) - 2/90 (2%) 37/95 (41%) 74/97 (80%)

 **N-formyl-4-chloro-o-toluidine**

 Male 0/46 (2%) - 0/49 (0%) 15/48 (38%) 40/47 (89%)

 Female 0/47 (0%) - 0/47 (0%) 23/43 (56%) 38/48 (79%)

 Total 1/93 (1%) - 0/96 (0%) 38/91 (47%) 78/95 (84%)

 **4-Chloro-o-toluidine**

 Male 0/50 (0%) 0/47 (0%) 4/48 (8%) 23/47 (48%) 40/48 (83%)

 Female 1/45 (7%) 1/45 (2%) 3/48 (6%) 30/47 (62%) 34/49 (72%)

 Total 1/95 (1%) 1/92 (1%) 7/96 (19%) 53/94 (66%) 74/97 (78%)

 to shorten the latent period for tumour formation and also to hasten

 the malignant progression of existing neoplasms in the skin. At

 500 mg/kg body weight, the time of first appearance of tumours was 483

 days without croton oil and 154 days with croton oil. The latency

 period also decreased with increasing dose levels of chlordimeform. In

 the liver, changes consisted of enlargement, hepatocytic hyperplasia,

 and hepatocytic carcinomas.

 In a carcinogenicity study by Sachsse et al. (1978a), groups of

 mice (50/sex/group; Tif: MAG strain) were fed N-formyl-4-chloro- o-

 toluidine in the diet at concentrations of 0, 20, 100 and 500 mg/kg

 for 24 months. After this time, all animals were fed a control diet

 until the study was concluded when 90% of the animals in a group had

 Table 12. Incidence of tumours in mice after dietary administration of chlordimeform or 4-chloro-o-toluidine (Li et al., 1985a)

 Dietary Number of animals Number of animals Incidence Number of animals Incidence Days to

 concentration necropsied bearing haemangiomas (%) bearing (%) appearance of

 (mg/kg diet) or haemangiosarcomas haemangiosarcomas neoplasm

 **Chlordimeform**

 0 50 0 0 0 0 -

 20 50 8 16 0 0 494

 100 50 22 44 5 10 469

 300 50 36 72 15 30 448

 **4-Chloro-o-toluidine**

 300 50 31 62 13 26 283

 Table 13. Incidence of tumours in mice following dermal application of chlordimeform (Jiang et al., 1988)

 Group/treatment Skin Liver

 Number Carcinomas Papillomas Hyperplasia Number Carcinomas Papillomas Hyperplasia

 of animals (%) (%) (%) of animals (%) (%) (%)

 Water 18 0.0 0.0 6.1 17 0.0 0.0 0.0

 Croton oil alone 17 0.0 0.0 17.6 24 0.0 0.0 8.3

 100 mg/kg + croton oil 19 0.0 5.3 21.1 21 23.8 0.0 9.5

 500 mg/kg 22 4.6 4.6 18.2 20 25.0 0.0 0.0

 chlordimeform alone

 500 mg/kg + croton oil 23 4.4 4.4 52.2 25 8.0 0.0 4.0

 2000 mg/kg + croton oil 15 20.0 20.0 26.7 14 14.3 0.0 0.0

 4000 mg/kg + croton oil 15 60.0 13.3 13.3 16 18.8 6.2 0.0

 Coal tar pitch 18 88.9 11.1 0.0 19 15.8 5.3 0.0

 died. There was no sign of adverse behaviour, and acute mortality was

 not noted. Growth and food consumption were unaffected. There were

 significant differences noted in survival after one year of age. Both

 males and females showed an increased mortality at 100 and 500 mg/kg

 after approximately one year of feeding. The onset of increased

 mortality occurred earlier in females. The females at the 20 mg/kg

 dietary level showed a slightly higher, non-significant, mortality

 during the same period. Detailed gross and microscopic examination of

 a variety of tissues and organs showed the presence of numerous gross

 anatomical lesions. There was an increased number of haemorrhagic

 masses in the subcutaneous tissues in the retroperitoneum and in some

 internal organs of mice at all treatment levels. Detailed microscopic

 examination confirmed that the increased incidence of haemorrhagic

 masses were malignant tumours of vascular origin. These tumours were

 histologically classified as malignant haemangioendotheliomas (see

 Table 11). In addition to the occurrence of tumours, the time to

 tumour relationship was decreased as the dietary concentration was

 increased. Other neoplasms occurring in the study were not considered

 to be treatment-related. A no-observed-effect-level was not

 demonstrated under the condition of this experiment.

 The carcinogenicity of 4-chloro -o-toluidine has been examined

 in four dietary studies.

 An early study by Ezumi and Nakao conducted in 1974 was reviewed

 by the JMPR in 1978 and considered inadequate (FAO/WHO, 1979).

 In a large study on the carcinogenicity of 21 aromatic amines and

 their derivatives described by Homburger et al. (1972) and Weisburger

 et al. (1978), groups of CD-1 mice (25/sex/dose level) were

 administered 4-chloro- o-toluidine in the diet at dose levels of 0,

 750 or 1500 mg/kg for males, and 0, 2000 or 4000 mg/kg for females for

 a period of 18 months. All mice were placed on a control diet for an

 additional 3 months before sacrifice and complete necropsy and

 histopathological examination of tissues. The incidence of

 haemangioendotheliomas was increased in males at both low (12/20) and

 high (13/20) dose levels compared to concurrent controls (0/14) and

 historical controls (5/99), and in females at both low (18/19) and

 high (12/16) dose levels compared to concurrent controls (0/15) and

 historical controls (9/102).

 In a study by Sachsse et al. (1978b), groups of mice

 (50/sex/group; Tif: MAGf strain) were fed a diet containing

 4-chloro- o-toluidine at concentrations of 0, 2, 20, 100 and

 500 mg/kg for 24 months. After 24 months, all animals were fed control

 diets until the study was concluded when 90% of the animals in a group

 had died. There were no overt signs of toxicity. Growth and food

 consumption were unaffected by treatment. An adverse effect on

 longevity (lifespan) was noted in both males and females at the two

 highest dietary levels. At the conclusion of the study upon gross

 examination there was a marked increase number of haemorrhagic masses

 in subcutaneous tissue, in the retroperitoneum, and in some internal

 organs. Microscopic examination revealed an increased incidence of

 haemorrhagic malignant tumours of vascular origin at dose levels of

 20 mg/kg and above (see Table 11). The tumour incidence in control

 exceeded the incidence observed at 2 mg/kg. The tumours were

 histologically classified as malignant haemangioendotheliomas and, on

 occasion, metastases were observed. There was not only a significant

 dose-dependent increase in the total incidence of malignant tumours

 but the time to appearance of tumours occurred at a markedly earlier

 date in animals at the higher concentrations than in those at the

 lower concentrations. A benign variant of the haemangioma was observed

 in all groups, and although without the characteristics of malignancy,

 did cause local invasion. Thus, the benign and malignant tumours have

 been grouped together. The vascular tumours (haemangiomas and

 haemangioendotheliomas) of the type that occurred in the mice appeared

 to be peculiar to this rodent species. The occurrence of other types

 of neoplasms in the study was not influenced by the presence of

 4-chloro- o-toluidine in the diet. Under the conditions of this

 experiment, 2 mg/kg in the diet appeared to be a no-observed-effect

 level.

 In a study with 4-chloro- o-toluidine conducted by the National

 Cancer Institute (NCI, 1979), groups of B6C3F1 mice (50/sex/dose

 level) were administered 4-chloro -o-toluidine in the diet at dose

 levels of 3750 or 15 000 mg/kg for males and 1250 or 5000 mg/kg for

 females for 99 weeks. Control groups consisted of 20 males and 20

 females. There was a dose-related increase in mortality in both sexes.

 There was also a dose-related increase in the incidence of

 haemangiosarcomas as shown in Table 14. The haemangiosarcomas

 apparently originated in fatty tissue adjacent to the genital organs

 and not in a particular organ. In some instances, they were observed

 to infiltrate the abdominal muscles, uterus, ovary, prostate or

 urinary bladder. The haemangiosarcomas were lethal to 89 (75%) of the

 affected mice, owing to haemorrhage in the peritoneal cavity and to

 the space-consuming character of the lesions. Pulmonary metastasis was

 observed in only 5 (4%) of the 119 dosed animals bearing

 haemangiosarcomas. Associated pathological alterations that were

 recorded at necropsy were haemorrhage in the peritoneal cavity and

 variable enlargement of the spleen. It was concluded that 4-chloro-

 o-toluidine was carcinogenic in B6C3F1 mice.

 In the study of Li et al. (1985a), a single dietary dose of

 4-chloro- o-toluidine (300 mg/kg) was given to mice for 18 months as

 a positive control. The incidence of tumours was similar to that seen

 in mice receiving 300 mg/kg of chlordimeform, but the latency period

 was considerably reduced (Table 12).

 Table 14. Incidence of tumours in mice following dietary

 administration of 4-chloro-o-toluidine (NCI, 1979)

 Male Female

 Control 3750 15 000 Control 1250 5000

 mg/kg mg/kg mg/kg mg/kg

 Number of animals 20 50 50 18 49 50

 Haemangiosarcomas 0 3 37 0 40 39

 (0%) (6%) (74%) (0%) (82%) (78%)

 Haemangioma 0 3 5 1 6 0

 (0%) (6%) (10%) (6%) (12%) (0%)

 7.7.2 Rat

 The carcinogenicity of chlordimeform and its metabolites has

 generally been considered as part of more detailed long-term studies

 (see Section 7.3). In the studies below, carcinogenicity was the

 primary consideration.

 In a study conducted by the National Cancer Institute (NCI,

 1979), groups of F344 rats (50/sex/dose level) were fed a diet

 containing 4-chloro- o-toluidine at concentrations of 1250 mg/kg or

 5000 mg/kg for 107 weeks. Control groups contained 20 animals of each

 sex. There was no significant dose-related trend in mortality in

 either sex. There was a variety of neoplastic and non-neoplastic

 changes in control and treated rats. There was a small increase in

 adenomas of chromophobe cells of the pituitary gland in both male and

 female rats compared to controls (see Table 15). All of these tumours

 were benign, are also common in this strain of rat and have occurred

 in 21% of control female rats in the NCI laboratories. The authors

 concluded that on the basis of histopathological examination,

 4-chloro- o-toluidine was not carcinogenic in F344 rats.

 In a large study on the carcinogenicity of 21 aromatic amines and

 their derivatives by Weisburger et al. (1978), groups of male Charles

 River CD rats were administered 4-chloro- o-toluidine in the diet at

 dose levels of 0, 2000 or 4000 mg/kg diet for the first 3 months,

 which was then reduced to 0, 500 or 1000 mg/kg diet for the following

 15 months. There was no statistically significant increase in tumours

 in either of the treated groups.

 Table 15. Incidence of tumours in rats following dietary

 administration of 4-chloro-o-toluidine (NCI, 1979)

 Male Female

 Control 1250 5000 Control 1250 5000

 mg/kg mg/kg mg/kg mg/kg

 Number of animals 19 48 47 19 48 48

 Chromophobe 2 6 15 1 13 15

 adenoma (11%) (13%) (32%) (5%) (27%) (31%)

 Chromophobe 0 0 2 0 3 1

 hyperplasia (0%) (0%) (4%) (0%) (6%) (2%)

 7.8 Other special studies

 7.8.1 Immunotoxicity

 In a study by Wiltrout et al. (1978), the potential of various

 pesticides to influence the primary humoral immune response in the

 mouse with respect to both dose and time of exposure was examined.

 Mice receiving a single oral dose of chlordimeform at approximately

 the LD50 level (148 mg/kg body weight) experienced a significant

 suppression of humoral response when the dose was administered on the

 day of immunization or two days after immunization. No response was

 observed at one tenth of the LD50 dose, even when administered for

 8 or 28 days.

 Further studies by Shopp et al. (1985) investigated the effect of

 chlordimeform on both humoral and cell-mediated immunity in the mouse

 following both acute and 14-day exposures by the intraperitoneal

 route. There was a decrease in IgM antibody-forming (plaque-forming)

 cells when measured 4 days after intraperitoneal administration at 20

 or 40 mg/kg body weight per day. These dose levels did not result in

 any alteration of cell-mediated immunity. When administered orally,

 chlordimeform at doses as high as 120 mg/kg body weight per day did

 not have any effect on the 4- or 5-day antibody response.

 Immunological parameters that may be related to the carcinogenic

 activity of chlordimeform in rats were investigated by Thomas et al.

 (1990). These included spleen/body weight ratio, splenocyte viability,

 T and B cell mitogenesis, natural killer (NK) cell and natural

 cytotoxic (NC) cell activity. Chlordimeform was administered

 intraperitoneally on three consecutive days at 0, 1, 10 or 75 mg/kg

 body weight per day. 4-Chloro- o-toluidine was administered

 intraperitoneally on three consecutive days at 0, 10, 50 or 100 mg/kg

 body weight per day. Spleen/body weight changes were observed only at

 the highest dose of chlordimeform. No changes were observed with

 either chemical on splenocyte viability or T and B cell mitogenesis.

 An inhibition of NC activity at all chlordimeform doses was observed,

 and an inhibition of NK activity was observed at 10 mg/kg body weight

 per day and above. The relevance of this result to the carcinogenic

 activity of these chemicals is doubtful.

 7.8.2 Behavioural effects

 Behavioural studies of the effects of chlordimeform in rats were

 first investigated by Olson et al. (1978). The effects of exposure

 prenatally and post-natally were examined following a dietary intake

 of 0.1 mg/kg body weight per day. Early development testing (swimming

 and righting reflex) was conducted on rat pups from post-natal days 7

 to 17, while motivational, learning and retention tests were conducted

 on days 70 to 90. The most significant differences between control and

 treated groups was in the swimming task, retarded maturation being

 observed in the chlordimeform-fed group. There was no treatment-

 related effect with regard to maze tests or with regard to the tests

 of motivation.

 Moser et al. (1988) examined the behaviour of rats using a

 functional observation battery following a single oral administration

 of chlordimeform at dose levels of 0, 1, 25 or 56 mg/kg body weight.

 Rats were examined at 1, 5 or 24 h. Chlordimeform produced a decrease

 in body weight as well as a decrease in body temperature. There was a

 dose-related increase in general activity, CNS excitability and

 sensory responsiveness, coupled with a decrease in rearing, gait and

 arousal. Chlordimeform also produced an increase in grip strength.

 Other behavioural effects observed with chlordimeform have

 included appetite stimulation in rats (Pfister et al., 1978b), flavour

 aversion in both rats (MacPhail & Leander, (1980) and mice (Leander et

 al., 1984) and alteration in schedule-controlled performance in rats

 (MacPhail & Leander, 1981), mice (Glowa, 1986) and pigeons (Leander &

 MacPhail, 1980). Witkin & Leander (1982) also demonstrated that, while

 causing appetite stimulation in rats, chlordimeform produced a dose-

 related decrease in water consumption, in contrast to other appetite

 stimulants.

 7.8.3 Pharmacological and biochemical effects

 The pharmacological and biochemical effects of chlordimeform in

 animals have been reviewed by Knowles (1991).

 The cardiovascular effects of chlordimeform treatment were

 recognized from an early stage with the observation that chlordimeform

 administered intraperitoneally to rabbits caused a marked decrease in

 arterial blood pressure of almost 50% within 30 min of treatment

 (Matsumura & Beeman, 1976). Cardiovascular changes were also noted in

 the dog (Lund et al., 1979a,b; Rieger et al., 1981) but in this case

 the effect was biphasic, consisting of an initial depressor response

 associated with decreased cardiac contractility and vascular

 resistance, and a secondary pressor response associated with increased

 cardiac contractility and vascular resistance. These actions of

 chlordimeform were noted to be similar to those of local anaesthetics

 such as procaine and lidocaine (Pfister et al., 1978a; Lund et al.,

 1979a,b,c).

 In studies by Watkinson (1985, 1986a,b), the effects of

 chlordimeform on cardiovascular functional parameters were examined in

 post-weaning and geriatric rats following intravenous treatment at

 dose levels up to 60 and 120 mg/kg body weight, respectively, or

 intraperitoneal treatment of post-weaning rats at dose levels up to

 60 mg/kg body weight. Chlordimeform produced profound and abrupt

 decreases in heart rate and blood pressure within 3 min, together with

 multiple arrhythmias and alterations in electrocardiogram waveforms

 and intervals. The effects observed in post-weaning rats were less

 severe than those observed in geriatric rats.

 The inhibition of monoamine oxidase in rats in vivo and

 in vitro by chlordimeform and/or its metabolites has been

 extensively studied (Beeman & Matsumura, 1973; Maitre et al., 1978;

 Benezet et al., 1978; Hollingworth et al., 1979; Kadir & Knowles,

 1981; Kaloyanova et al., 1981; Bailey et al., 1982). The lack of

 correlation of toxicity of chlordimeform metabolites to monoamine

 oxidase inhibition and the fact that chlordimeform is a relatively

 weak monoamine oxidase inhibitor suggest that monoamine oxidase

 inhibition is not the primary factor involved in the acute toxicity of

 chlordimeform (Neumann & Voss, 1977; Robinson & Smith, 1977;

 Hollingworth et al., 1979).

 Chlordimeform also has an effect on the level of biogenic amines

 in brain and plasma of rats, which may in part at least be due to

 the inhibition of monoamine oxidase levels. Administration of

 chlordimeform to rats was found to produce an increase of 25-70% in

 5-hydroxytryptamine, norepinephrine or dopamine levels in brain

 (Maitre et al., 1978; Benezet et al., 1978; Bailey et al., 1982).

 However, Johnson & Knowles (1983) treated rats subcutaneously with

 chlordimeform (200 mg/kg body weight) and found no change in any of

 the amines.

 Chlordimeform and some of its metabolites have been shown to

 affect platelet function, as measured by the uptake of radioactive

 5-hydroxytryptamine (Knowles, 1991).

 Chlordimeform also has antipyretic and anti-inflammatory actions,

 as shown by its ability to reduce yeast-induced fever in rats. It also

 antagonizes both early (5-hydroxytryptamine- and histamine-mediated)

 and late (prostaglandin-mediated) phases of carrageenan-induced

 hind-paw oedema, albumin-induced oedema, and oedema induced by direct

 injection of 5-hydroxytryptamine and histamine (Yim et al., 1978).

 Chlordimeform also induced mild gastric ulceration in rats after

 intraperitoneal injection (20-80 mg/kg body weight) but not after oral

 treatment (80-240 mg/kg body weight). The above actions may be related

 to the ability of chlordimeform to inhibit prostaglandin biosynthesis

 (Yim et al., 1978; Holsapple & Yim, 1981).

 Chlordimeform induces hypothermia in rats (Watkinson & Gordon,

 1987) and mice (Gordon et al., 1985). Watkinson et al. (1989)

 examined the effect of core body temperature on both the survival

 and cardiovascular functions of rats following treatment with

 chlordimeform. The results indicated that at a given dose of

 chlordimeform, the magnitude and duration of the observed toxic

 effects are primarily a function of core body temperature. The authors

 concluded that moderate hypothermia, but not extreme hypothermia, may

 have a beneficial effect with respect to survival after exposure to

 chlordimeform.

 Chlordimeform has been shown to have an effect on both visual and

 auditory functions in mammals. Intraperitoneal treatment of male rats

 with acute dosages of chlordimeform (5-40 mg/kg body weight) before

 testing revealed a temporary increase in both the amplitude and

 latency of pattern reversal-evoked potentials and an increase only in

 the latency of pattern flash-evoked potentials (Dyer & Boyes, 1983;

 Boyes & Dyer, 1984). Boyes & Moser (1988) provided evidence to support

 the hypothesis that these effects are evoked through actions as a

 central nervous system alpha-adrenegic agonist. Janssen et al. (1983)

 demonstrated effects on the brain stem auditory-evoked response after

 injection of chlordimeform at a dose levels of 40 mg/kg body weight.

 It has been suggested that these effects may by secondary to the

 hypothermic effects induced by chlordimeform (Gordon et al., 1985).

 Chlordimeform has been shown to affect the activity of hepatic

 drug-metabolizing enzymes in both rats and mice. Studies have been

 conducted following gastric intubation at dose levels up to 150 mg/kg

 body weight per day for 7 days, and also following intraperitoneal

 injections either singly (100 mg/kg body weight) or daily (75 mg/kg

 body weight per day) for 4 days. Chlordimeform treatment induced

 several of these hepatic drug-metabolizing enzymes with significant

 species and/or sex specificity. Cytochrome P-450 content was increased

 in all cases.

 7.9 Factors modifying toxicity

 The factors modifying the acute toxicity of chlordimeform have

 been reviewed by Knowles (1991).

 7.10 Mechanisms of toxicity - mode of action

 7.10.1 Mechanism of acute toxicity

 A large number of studies that investigated the mechanism of

 action following acute poisoning with chlordimeform have been

 reported.

 Based on the early in vitro and in vivo studies of Aziz &

 Knowles (1973) and Beeman & Matsumura (1973), it was suggested that

 the increase in biogenic amines resulting from inhibition of monoamine

 oxidase by chlordimeform could account for the variety of toxic signs

 following acute poisoning. However, Maitre & Gfeller (1975) and

 Robinson et al. (1975) demonstrated that this mechanism does not play

 a significant role in the acute toxicity in rats.

 A number of other studies have attempted to define the mode of

 action of chlordimeform. Studies in insects have shown that

 chlordimeform has little activity on cholinergic transmission although

 it is an uncoupler of oxidative phosphorylation and an inhibitor of

 electron transport (Abo-Khatwa & Hollingworth, 1972a). A number of

 biochemical mechanisms have been postulated to explain the effects of

 chlordimeform in insects, including uncoupling of respiration

 (Abo-Khatwa & Hollingworth, 1972a,b), inhibition of monoamine oxidase

 (Knowles & Roulston, 1972) and blockage of neuromuscular transmission

 (Wang et al., 1975; Watanabe et al., 1975), and motor stimulation

 through actions on central non-cholinergic synapses (Lund et al.,

 1979a; Lund et al., 1979c). The latter effect is thought to be

 mediated through the neurotransmitter, octopamine (Lund et al.,

 1979b). Both chlordimeform and particularly demethylchlordimeform have

 been shown to interact with the octopamine receptor and partially

 mimic the pharmacological effects of octopamine (Evans & Gee, 1980;

 Nathanson & Hunnicutt, 1981; Bokisch et al., 1985).

 In mammalian systems, oxidative phosphorylation is uncoupled

 (Abo-Khatwa & Hollingworth, 1972b) and RNA synthesis is inhibited by

 chlordimeform, but only at very high concentrations (Murakami &

 Fukami, 1974). The effects of chlordimeform on hepatic drug-

 metabolizing enzymes was dependent on both sex and species and did not

 show any particular pattern that would indicate a consistent mechanism

 of action (Budris et al., 1983; Bentley et al., 1985; Leslie et al.,

 1988).

 Chlordimeform, acting as a direct depressant on cardiac and

 vascular muscle, induced a hypotensive state in dogs. Chlordimeform

 did not interfere with the autonomic nervous system. The mechanism of

 cardiovascular depression may be related to that noted with frog nerve

 preparations treated with procaine, a local anaesthetic. The

 metabolite, 4-chloro- o-toluidine has been shown to interfere with

 rat cardiac receptors (Wang et al., 1975; Watanabe et al., 1975;

 Matsumura & Beeman, 1976; Knowles, 1976; Hollingworth, 1976; Lund et

 al., 1978a).

 More recent research has shown that formamidine pesticides may

 exert their effects on the central nervous system by interacting

 directly with adrenergic receptors, particularly the alpha-2 subtype

 (Costa & Murphy, 1987; Costa et al., 1988, 1989). This interaction

 appears to mediate several of the observed effects of formamidines,

 such as changes in heart rate (Hsu & Kakuk, 1984, Watkinson, 1985;

 1986a,b), pupil diameter (Hsu & Kakuk, 1984), visual evoked potential

 (Boyes & Moser, 1988) and hormonal secretion (Goldman et al., 1990;

 1991). Costa et al. (1991) demonstrated that chlordimeform

 decreases the hepatic glutathione content by up to 40% in a

 time- and dose-dependent manner, through an interaction with

 alpha2-adrenoreceptors. Wu et al. (1990) have demonstrated that

 chlordimeform inhibits the binding of the known alpha2-adrenoreceptor

 blockers, clonidine and yohimbine, in rat forebrain tissue

 in vitro. Furthermore, Stoker et al. (1991), in a further study on

 the effects of chlordimeform on hormone release, have demonstrated in

 rats, treated intraperitoneally with chlordimeform (20 or 50 mg/kg

 body weight), that there is an increase in adrenocorticotropic hormone

 (ACTH), circulating corticosteroid (CORT) and prolactin (PL) in a

 dose-dependent manner. alpha-Adrenergic agonists specifically

 inhibited these effects indicating the interference with a regulatory

 signal mediated by alpha-adrenergic receptor-associated activity.

 Candura et al. (1992) demonstrated that the inhibition induced by

 chlordimeform in the intestinal tract is mediated by calcium channel

 blockade rather than by alpha2-adrenoceptor activation. In a study by

 Robinson et al. (1975), it was found that using drugs to block the

 serotonergic or alpha-adrenergic receptors did not reduce the

 chlordimeform-induced lethality in male rats.

 7.10.2 Mechanism of carcinogenicity

 Chlordimeform and its metabolites, N-formyl-4-chloro- o-

 toluidine and 4-chloro -o-toluidine, have been shown to induce mouse

 tumours of a vascular origin characterized histologically as

 haemangioendotheliomas and haemangiosarcomas. 4-Chloro- o-toluidine

 has been shown to be a more potent carcinogen than chlordimeform, both

 with respect to dose-response and to a reduced latency period.

 Haemangioendotheliomas and haemangiosarcomas were not induced in rats.

 Cases of bladder cancer in humans associated with occupational

 exposure to high levels of chlordimeform or 4-chloro- o-toluidine

 have been seen in groups with high urinary levels of chlordimeform and

 4-chloro- o-toluidine.

 The exact mechanism of induction of these tumours is unknown but

 there is evidence that a genetic mechanism involving mutations induced

 by 4-chloro- o-toluidine is involved.

 Metabolic studies in mice and rats indicate a similar metabolic

 pathway for chlordimeform in both species. The kinetics of absorption

 and elimination in mice and rats also seem to be similar. However, the

 overall DNA binding was higher in mice than rats, and one DNA adduct

 was formed to a 6- to 30-fold higher extent in mice.

 There is considerable evidence that 4-chloro- o-toluidine causes

 severe toxic effects in the human bladder leading to haemorrhagic

 cystitis (see section 8). Monitoring of urinary metabolites in humans

 also indicates that chlordimeform is rapidly metabolized to 4-chloro-

 o-toluidine in vivo.

 4-Chloro- o-toluidine also has a close structural similarity

 to aromatic amines for which there is established evidence of

 carcinogenicity by animal experimentation and also by human

 epidemiological data (Parkes, 1984).

 Taken together, the evidence strongly implicates 4-chloro- o-

 toluidine as the causative agent in the induction of tumours in both

 mice and humans. A proposed route of activation that may be associated

 with carcinogenicity is shown in Fig. 2. However, the mechanism of the

 carcinogenicity remains unclear.

 

 8. EFFECTS ON HUMANS

 8.1 General population exposure

 8.1.1 Acute poisoning incidents

 The most comprehensive data on acute poisoning cases associated

 with exposure to chlordimeform has come from China. Details of these

 published poisoning cases are shown in Table 16. While many were due

 to intentional ingestion, there were also cases of unintentional

 poisoning as a result of consumption of contaminated food, as well as

 occupational exposure to the spray. In a brief report prepared by Deng

 et al. (1984) of a 1983 symposium in Hu-bei Province on chlordimeform

 poisoning, which featured some 29 papers and 859 case studies, it was

 stressed that the main cause of death was suppression of cardiac

 contracture and dilation of blood vessels resulting in circulatory

 failure.

 Arima et al. (1976) described an unsuccessful suicide attempt

 involving a 76-year-old male who ingested 100 g chlordimeform. He

 vomited several times before arriving at hospital 50 min after

 ingestion. He was lethargic with a weak pulse and cyanosis associated

 with his lips, nails and skin. Methaemoglobin levels represented 17%

 of total haemoglobin at 5 h but returned to normal levels by 2 days.

 He regained consciousness by 50 h, although complained of headache and

 blurred vision. The only treatment received was gastric lavage, which

 was performed shortly after his arrival at the hospital.

 8.2 Occupational exposure

 8.2.1 Acute poisoning incidents

 Currie (1933) reported nine cases of haematuria in workers

 exposed to 4-chloro- o-toluidine (erroneously called 5-chloro- o-

 toluidine) by inhalation or possibly by absorption through the skin.

 All patients had difficulty urinating and had suprapubic pain. Most of

 the workers were exposed to the material for only 1-2 days. Despite

 efforts to control exposure to the chemical in the factory, further

 cases of poisoning occurred, and manufacture was ceased. In a

 follow-up study of three of the nine cases after 3 years, one patient

 had no bladder trouble, one had a slight cystitis and urethritis, and

 one had carcinoma of the bladder.

 Jurincic et al. (1991) reported cases of acute haemorrhagic

 cystitis in two men (aged 19 and 50) following involvement in cleaning

 of a water-tank that had likely been used to transport chlordimeform.

 Both developed abdominal pain, dysuria and haematuria in the evening

 following exposure. Cystoscopy revealed haemorrhagic cystitis,

 which was confirmed by bladder mucosa biopsy. Serum levels of

 4-chloro- o-toluidine (referred to as 4-chloro-2-methylaniline) were

 >1 mg/litre in both patients and urine levels were 16 mg/litre in the

 Table 16. Case studies of acute chlordimeform poisoning in China

 Study Number of patients Route of exposure Number Clinical features Reference

 number (sex and/or age) of deaths

 1 71 4 dermal absorption 5 ECG: 26 tachycardia; 6 bradycardia; 11 ectopic Wang & Tong (1992)

 (28 male, 67 ingestion rhythm; 6 premature beat; 2 atrial fibrillation;

 43 female) ventricular fibrillation; 1"Torsade de Pointes";

 2 high pike P, 6 A-V block, 17 S-T depression,

 3 inverse T, 1 S-T elevation ,7 Q-T elongation.

 In 33 severe cases, 28 has ECG abnormalities;

 38 moderate cases, 14 had abnormal ECG. Changes

 in heart were found in 32 cases. Deaths were from

 respiratory failure (3); ventricular fibrillation

 (1) and supraventicular tachycardia (1).

 2 4 ingestion(?) 0 Mild cyanosis, cystitis (2 cases occupational, Nui et al. (1990)

 2 cases non-occupational; OPs also in formulation.

 3 1 female ingestion 0 Jaundice on 3rd day which progressively deepened. Liu et al. (1990)

 (30 years old) (150 ml) Hb 40 g/litre (70 g/litre on admission); complete

 recovery, discharged on day 20.

 4 52 ingestion 0 Loss of appetite (86.5%), urgency in urination He (1989)

 (19 male, (20-350 ml) (84.6%), cyanosis (81.1%), coma (67.3%), miosis

 33 female) (34.6%), mydriasis (15.4%),hypotension (38.5%),

 tachycardia (32.7%), bradycardia (3.8%).

 Impairment of liver and renal functions. 15 ECGs:

 7 tachycardia, 2 bradycardia, Q-T elongation,

 8 T-wave changes. Treated with methylene blue,

 vitamin C, fresh blood transfusion and sopolamine.

 Table 16. (con't)

 Study Number of patients Route of exposure Number Clinical features Reference

 number (sex and/or age) of deaths

 5 35 ingestion(?) 0 18 severe cases. Suggested use of 5-36 mg He et al. (1987)

 atropine for chlordimeform poisoning and

 50-128 mg for mixed pesticide poisoning.

 6 1 female ingestion 0 Cyanosis, pin-point myosis. Given atropine Zhou (1987)

 (30 years old) (80 ml 25% (15 mg/min) after lavage until total of 530 mg.

 chlordimeform) Symptoms indicated overdose of atropine. Methylene

 blue given, recovery and discharge at day 7.

 7 23 4 contaminated food; 3 Mild case: nausea, vomiting, light cyanosis,

 (6 male, 19 ingestion no somnolence. Moderate case: somnolence and Xu (1987)

 17 female) (10-350 ml) light consciousness. Severe case: Marked

 cyanosis, coma, shock. 5 ECG examined:

 2 bradycardia, 1 tachycardia, A-V block,

 S-T change. Mild impairment of liver renal

 functions. Treated with methylene blue,

 19 recovered.

 8 1 female ingestion 0 Lavage and treatment led to recovery from danger. Liu & Li (1987)

 (52 years old) (30 ml conc. Black stool, tachycardia occurred on 3rd day.

 formulation) Complete recovery.

 9 187 27 occupational spray; 13 Cyanosis (63.6%), nausea (49.2%), vomiting Ding & Huang (1987)

 (66 male, 16 ingestion (20-250 ml (44.9%), mydriasis (32.1%), somnolence (33.7%),

 121 female) 25% chlordimeform coma (32.1%), irritation in urination (30.5%),

 formulation) hypotension. 27 ECGs: 4 tachycardia, 6 bradycardia,

 4 S-T & T wave change, 2 pre-mature beat, 2

 conductive blockage. 158 cases received methylene

 blue and 174 recovered within 1-5 days.

 Table 16. (con't)

 Study Number of patients Route of exposure Number Clinical features Reference

 number (sex and/or age) of deaths

 10 1 male occupational spray 0 Sprayed incorrect dilution spray. Complained of Gu et al. (1987)

 (28 years old) fatigue, somnolence, loss of appetite, nausea,

 vomiting, but no cyanosis, or signs of cystitis,

 pulse 68, BP 128/94 (normally 120/80), MAO 25.12 U

 (normally 38.87 U). Total chlordimeform in urine

 on admission, 6.4 mg/ml. Recovered quickly.

 11 6 (?) ? Main clinical features: drowsy, cyanosis, Chan (1985)

 loss of consciousness, mydriasis, cystitis,

 hypotension, bradycardia, myocarditis, shock,

 methaemaglobinaemia.

 12 47 ingestion 4 Symptoms: drowsy, cyanosis, cystitis, Ke (1985)

 (11 male, 20-1900 ml 2 hypotension (severe case), 8 hypertension,

 36 female) 10 ECG: 1 tachycardia and T-wave change.

 13 25 ingestion(?) 1 Cyanosis, cystitis, hypotension, arrhythmia, Wang & Dong (1985)

 S-T and T changes, Q-T elongation. Treatment

 with gastric lavage, methylene blue, vitamin C

 14 682 340 occupational spray; 25 279 cyanosis, 147 cystitis, 197 somnolence, Liu & Zhang (1985)

 (331 male, 342 ingestion 211 coma, 81 shock, 109 tachycardia,

 351 female) 64 bradycardia, 54 hypertension, 22 hypotension.

 59 ECG: 8 premature beat, 4 Q-T elongation,

 16 S-T and T changes.

 15 358 283 ingestion 37 Somnolence, cyanosis, loss of appetite, Ding & Ru (1985)

 haemorrhagic cystitis, often myocardium damage,

 A-V block, cardiac failure.

 Table 16. (con't)

 Study Number of patients Route of exposure Number Clinical features Reference

 number (sex and/or age) of deaths

 16 49 3 occupational 4 13 cases were severe. Clinical features: cyanosis Liu & Ke (1985)

 46 non-occupational and cystitis with haematuria in all cases, most

 with severe somnolence and a few with coma. Two

 severe cases had hypothermia. Hypertension was more

 common than hypotension. 10 ECGs: only one case of

 T-wave change and tachycardia. Treatment with

 methylene blue and lavage.

 17 1 ingestion (300 ml 25% 0 Coma and cyanosis. Sudden cardiac arrest during Yang (1984)

 (female, form.) lavage, rescued with mechanical respiration.

 25 years old) Recovered after 14 days.

 18 24 ingestion (15-150 ml 2 16 cyanosis, 14 drowsiness, 8 haematuria, Wu et al. (1983)

 (11 male, 25% form.) 6 methaemoglobin, 1 cardiac arrest, which

 13 female) recovered after resuscitation.

 19 101 35 occupational spray, 2 89 chlordimeform alone cases: 66% cyanosis, Xie (1983)

 (49 male, 66 ingestion; 32 comas, 14 cystitis, 14 hypotension, 3 cardiac

 52 female) chlordimeform +Ops) failure. 8 ECGs: 6 myocardium damage (changes in

 Q-T, S-T, and T waves). Treatment with methylene

 blue, vitamin. C. All recovered.

 12 cases with mixed pesticides (OPs and Ocs).

 20 1 ingestion 1 Loss of consciousness, cyanosis, mydriasis, Wu (1982)

 (female, 85 years) (30 ml) arrhythmia. ECG: bradycardia, T-wave changes.

 Died on day 6.

 Table 16. (con't)

 Study Number of patients Route of exposure Number Clinical features Reference

 number (sex and/or age) of deaths

 21 20 occupational spray 0 Farmers applied wrong dilution chlordimeform to Li et al. (1982)

 (18 male, 2 female) cotton for one day. 7 drowsy, 10 loss of appetite,

 4 cystitis. Symptomatic treatment. All recovered

 in 2-4 days.

 22 2 male ingestion (100 & 200ml) 0 Cyanosis, coma, respiratory-circulation failure, Zhang et al. (1976)

 cystitis during 2nd day. Treatment with

 methylene blue and atropine.

 23 1 male 100 ml 0 Deep cyanosis, pulse 166. Xia & Gao (1977)

 24 6 male occupational spray 0 Contamination of body surface and clothing. Su (1977)

 Symptoms from day 1-4: cyanosis, haemorrhagic

 cystitis, fatigue. Recovery after 18 days.

 25 2 male occupational spray 0 Clothing contaminated. Haemorrhagic cystitis, Anonymous (1977)

 no cyanosis, ECG normal. Symptomatically treated.

 26 4 male occupational spray 0 Clothing contaminated. Haemorrhagic cystitis, Ming (1977)

 cyanosis, somnolence, loss of appetite, haematuria,

 RBC in urine for 20 days. Treatment: vitamin C,

 antibiotics, coagulators.

 51-year-old patient. Case studies of chlordimeform poisoning in China

 due to occupational exposure are given in Table 17, together with a

 brief account of the clinical features observed.

 Table 17. Levels of urinary chlordimeform and its metabolites in hospitalized

 workers (3 days following exposure) (Folland et al., 1978)

 Worker Total aminesa Chlordimeform 4-Chloro-o-toluidine Conjugate

 (mg/litre) (mg/litre) (mg/litre) (mg/litre)

 1 11.0 1.10 3.75 6.25

 2 15.2 2.16 4.16 8.67

 3 2.6 0.04 1.25 1.17

 a Measured following hydrolysis with 10N NaOH and 2 h at 80°C.

 A brief account of the signs and symptoms of chlordimeform

 poisoning and suggested interventions has been provided by Xue &

 Loosli (1994).

 8.2.2 Effects of long-term exposure

 A report of an outbreak of haematuria in employees of a chemical

 packaging plant in the USA over a 4-day period in 1975 was first

 reported by Armstrong et al. (1975). Further details were described by

 Folland et al. (1978). Nine of 22 workers who packaged chlordimeform

 became severely ill with abdominal pain, dysuria, urgency to void, or

 haematuria. In the previous year, four workers who had packaged the

 chemical had similar symptoms. While six workers recovered within 7 to

 18 days, three were hospitalized with symptoms which lasted from one

 to two months. In these three workers, abnormalities noted were

 microscopic haematuria and pyuria, proteinuria, low creatinine

 clearance, elevated SGOT, prolonged BSP retention, elevated serum

 amylase level, small bladder capacity, ureteral reflux and an intense

 inflammatory reaction in three bladder biopsy specimens. The highest

 concentrations of total amines were found in the urine of workers who

 had become ill and were hospitalized. Low but measurable levels were

 also found in workers who had not become ill. The major part of the

 urinary amines was present as 4-chloro- o-toluidine or as conjugates.

 Urinary total amines (following hydrolysis with 10 N sodium hydroxide

 and 2 h at 80°C), as well as chlordimeform and 4-chloro- o-toluidine,

 were measured in the hospitalized cases and are shown in Table 17.

 The results of a monitoring programme on packaging workers in a

 chlordimeform plant in the USA during 1976 have been described

 (personal communication by J.W. Barnett, Ciba-Geigy Agricultural

 Division, Greenborough, North Carolina, USA, to the California

 Department of Food and Agricultural). The programme involved more than

 100 workers and over 800 urine samples, monitoring for the presence of

 red blood cells, for residues of chlordimeform metabolites, and for

 clinical signs of toxicity in workers. Residues in urine samples were

 reported to range from <0.05 to 50 mg/litre. There was no evidence of

 microscopic haematuria found in the samples analysed nor of any

 clinical signs of toxicity.

 Four separate incidents resulting in 7 cases of frank haematuria

 following industrial exposure were reported in the USA during the

 period 1980-1984 (personal communication by J.W. Barnett, Ciba-Geigy

 Agricultural Division, Greenborough, North Carolina, USA, to

 Ciba-Geigy Ltd., Switzerland). Chemical cystitis, confirmed by

 cystoscopy and biopsy, was diagnosed in one case while non-specific

 bladder mucosal lesions were found in another. Six cases required

 hospitalization, but all resolved after cessation of exposure.

 In a study by Maddy et al. (1986), the results of a programme of

 monitoring (1982-1985) the urine of more than 200 workers, who had

 received training in the use of chlordimeform on cotton in California,

 were described. Although urinalysis was unremarkable and no

 significant cytological changes were found, a single case of bladder

 cancer was detected in a pilot who had seven seasons of exposure to

 chlordimeform.

 By contrast, in the same period (1980-1984), no cases of

 chlordimeform-induced haematuria occurred at manufacturing plants in

 Switzerland and West Germany or formulation plants in Australia,

 Columbia, Central America, Mexico and the USA. No cases of haematuria

 reportedly resulted from application or use of chlordimeform in the

 field (Anon., 1985b; personal communications by F.E. Pfister and P.

 Duback (Ciba-Geigy Ltd., Agricultural Division, Switzerland) and by

 N. Reckefus and K. Kossmann (Schering Aktiengesellschaft Agrochemical

 Division, Berlin, Germany), 1985).

 In a study by Lu et al. (1981), data on the effects of

 chlordimeform exposure of factory workers in China was examined. In

 this study, conducted in 1974, the air concentrations in the factory

 were generally below 0.036 mg/m3, with shorter periods at higher

 levels (0.108-0.33 mg/m3), during specific tasks. Skin contamination

 on hands and forearms was 9.1 mg/h for chemical operators

 and 964.2 mg/h for packers. The urinary excretion levels of

 chlordimeform and 4-chloro- o-toluidine in controls were 0.015 and

 0.042 mg/litre, respectively; in chemical operators they were

 0.065 and 0.108 mg/litre, respectively; and in packers were 0.263 and

 0.398 mg/litre, respectively. The health of the workers was examined

 during the following 3 years (1974-1976). In 44-56 workers (equal

 number of each sex) at an average age of 32 years and working period

 of 2 years, the main finding were neurosis, sore throat and disorders

 of the nervous system. There were no treatment-related effects on ECG,

 liver function, clinical chemistry or urinalysis parameters.

 In the same report (Lu et al., 1981), the effect of chlordimeform

 exposure on rice field workers during 1974 was also examined. The

 air concentration in the breathing space in all cases was below

 0.02 mg/m3. Skin contamination was examined at the front of the

 thorax, on the right forearm and on the right thigh. The applicators

 applied chlordimeform for 4-5 h per day for 1-3 consecutive days,

 wearing shirts and shorts with no other protection. Skin contamination

 was from splash or from spray. The levels found from splash on thorax,

 forearm and thigh were 0.0436, 0.0303 and 0.131 mg/100 cm2 per h,

 respectively. The levels found from spray on thorax, forearm and thigh

 were 0.235, 0.299 and 0.804 mg/100 cm2 per h, respectively. Medical

 examination during 1974/1975 revealed complaints of light-headedness,

 headache, fatigue, nausea, abdominal pain, skin itching and burning

 sensation, and hypotension. There were no changes in ECG or blood

 chemistry, and no reported cases of acute intoxication.

 In a study by Li et al. (1985b), the health of 24 packers

 (9 male, 15 female) in a chlordimeform manufacturing plant in Jiang-su

 Province of China, was examined. The chlordimeform division of the

 factory started manufacturing in 1975 and continued to do so at the

 time of the study. The employees were working in the factory for

 between 3 months and 4 years (average 1.5 years). Another 24 employees

 from the kitchen and kindergarten served as controls. The air

 concentration of chlordimeform (9 samples over 3 consecutive days) was

 0.066 mg/m3 (range 0.017-0.121 mg/m3). Skin contamination of the

 hands and forearms was 110 µg/100cm2 (S.D. 39 µg/100 cm2). Urinary

 chlordimeform levels were 0.20 ± 0.13 mg/litre, and urinary

 4-chloro-o-toluidine levels were 0.48 ± 0.29 mg/litre. Medical

 examination revealed no difference between packers and controls with

 regard to symptoms, laboratory examinations including liver enzymes

 and urinalysis parameters, chest X-rays, ECG, or other parameters of

 cardiac function. The only symptom associated with exposure was skin

 rashes and itching in 21% of exposed individuals. There was no

 difference in the micronucleus counting in cultured peripheral

 lymphocytes between exposed and control groups, nor were there any

 positive mutagenicity results from urine samples with or without

 glucuronidase or sulfatase in the medium.

 In a further study in a Chinese chlordimeform manufacturing

 factory, the health of employees involved in chlordimeform production

 was studied for the 5-year period, 1977 to 1981 (Anon., 1985a). The

 urinary chlordimeform plus 4-chloro- o-toluidine levels of packers

 was the highest at 0.39 mg/litre, which significantly correlated with

 skin contamination but not with air concentration. The major medical

 findings were complaints of lightheadedness, disorders in sleep,

 memory impairment, fatigue, loss of appetite, skin rashes and itching,

 and skin spot pigmentation. There were no features of cystitis. ECG

 findings in 36 employees indicated premature beats, partial A-V block,

 tachycardia and bradycardia. There was no evidence of chromosome

 aberrations in metaphase chromosomes of cultured peripheral

 lymphocytes.

 In a study by Tao et al. (1985), the health of 61 employees

 (25 chemical operators, 36 packers) of a pesticide factory in China

 was examined. Chlordimeform was produced in the factory for 5 months

 per year. Air levels ranged from 0.074 to 0.160 mg/m3. Skin

 contamination of packers (2.99 mg/day) was higher than for

 hemical operators (0.784 mg/day). The urinary excretion rate of

 chlordimeform plus 4-chloro- o-toluidine in packers was also higher

 (0.513 mg/litre) than for chemical operators (0.206 mg/litre) or

 controls (0.055 mg/litre). Symptoms of exposure noted in packers

 included loss of appetite, fatigue, somnolence and skin rashes.

 Hepatomegaly was observed. There was no difference in blood pressure

 or heart rate. Abnormalities in ECG were noted in 10/61 exposed

 employees compared to 6/76 controls.

 In a study by Wang et al. (1987), the health of 16 applicators

 (8 males, 8 females) spraying chlordimeform in cotton fields in

 Xin-yang Farm in the Jiang-su Province of China over a 3-day period

 (July 1986) was examined. Air levels in the breathing zone were

 0.031 mg/m3 and the skin contamination was 4.17 mg per shift. Urinary

 levels of chlordimeform plus 4-chloro- o-toluidine ranged between 1

 and 3 mg/litre over the exposure period. A close correlation was noted

 between the level of chlordimeform on the skin and the levels of

 chlordimeform plus 4-chloro- o-toluidine in the urine. Rapid

 excretion of chlordimeform plus 4-chloro- o-toluidine was noted

 following exposure. There was no change noted in heart rate, blood

 pressure, monoamine oxidase activity or urinalysis between exposed

 individuals and controls. Mild chlordimeform exposure, however,

 appeared to be related to loss of appetite and drowsiness.

 In a study by Zhang et al. (1986a), conducted at the same farm

 over the same period, 13 applicators (7 male, 6 female, 20-41 years of

 age) were examined during spraying chlordimeform on cotton over three

 consecutive days. Protective measures included gauze mask, plastic

 gloves and plastic apron, although it was noted that extensive

 contamination occurred. Air levels in the breath zone on each of the

 three days were 0.011, 0.014 and 0.011 mg/m3, respectively. Skin

 contamination on each of the three days was estimated by the method of

 Zhang et al. (1986b) to be 10.99, 4.32 and 4.45 mg/person per day,

 respectively. Urinary chlordimeform plus 4-chloro- o-toluidine

 levels were measured over the 3 days of exposure and for 7 days

 after cessation of exposure. Urinary levels ranged from a peak of

 2.408 mg/litre during exposure to 0.036 mg/litre after 7 days.

 Excretion of chlordimeform occurred very rapidly with the highest

 level being detected in the sample collected at the end of each shift.

 There was a close correlation between skin contamination and urinary

 excretion. Metabolism occurred very rapidly since 4-chloro- o-

 toluidine usually accounted for 70-93 % of the total amount in the

 urine. Serum monoamine oxidase activity varied from 26.18 U to

 19.26 U. Clinical symptoms were somnolence, headache, dizziness and

 fatigue. Heart rate and blood pressure dropped on the 2nd and 3rd

 days. Analysis of ECG indicated elongation of P-R, Q-T intervals. One

 person complained of urgency and pain in urination, gross haematuria,

 and the urinary chlordimeform plus 4-chloro- o-toluidine level was

 more than 6 mg/litre. Another four subjects were found to have

 microscopic haematuria. Liver function tests were normal.

 In a study by Xue et al. (personal communication by S.-Z. Xue,

 M. Wang, C.-M. Chu and X.-W. Zhou entitled "Effects of chlordimeform

 on cardiovascular function in humans with occupational exposure",

 1993), the effect of chlordimeform on cardiovascular function was

 studied in exposed farm workers and in manufacturing workers in China.

 Four separate exposure groups were studied. The first (short-term)

 exposure group consisted of 16 farmers engaged in spraying

 chlordimeform (0.125% solution) in a cotton field. Exposure was for a

 3- to 4-h period for 3 consecutive days. The second (long-term)

 exposure group consisted of 21 chlordimeform packers in a factory who

 had worked for 6 months on this task. The third exposure group

 consisted of 19 factory plant operators who had minimal exposure to

 chlordimeform. The fourth group consisted of 9 control (non-exposed)

 factory workers. Exposure was measured in the breathing zone air

 (personal sampler for the working shift, usually 6 h), by dermal

 contact (pooled aliquot of 10 swabs from various body sites), and by

 urine measurements. In each case, chlordimeform and its major

 metabolite, 4-chloro- o-toluidine, were measured. The cardiovascular

 system function was determined by measurement of blood pressure, heart

 rate and electrocardiography (ECG). Exposure data indicated the packer

 group had a higher inhalation exposure (0.107 mg/m3) than the

 sprayers (0.031 mg/m3). Dermal exposure, on the other hand, was

 higher in the sprayers group (4.251 mg/m2) than in the packers group

 (2.713 mg/m2). Urinary levels collected at the end of the working

 shift indicated the highest level in sprayers (1.950 mg/litre)

 compared to packers (1.267 mg/litre) and operators (0.097 mg/litre).

 In the farmer group, analysis of cardiovascular activity indicated a

 significant decrease in heart rate, and an increase in P-wave

 duration, Q-T interval and amplitude of T-wave compared to the control

 group. In the factory workers, the packers had significantly lower

 diastolic and systolic blood pressure, and an increase in T-wave

 amplitude compared to the plant operators. The heart beat of packers

 was also higher than controls, but not significantly. The

 cardiovascular function parameters of the plant operators were

 slightly but not significantly different to those of controls.

 Examination of the cardiovascular function parameters of the

 packers during a month of continuous exposure indicated a relationship

 between length of exposure, total urinary chlordimeform, and cardiac

 function parameters (see Table 18). Analysis of the exposure-effect

 correlation indicated the drop in blood pressure was the most

 sensitive parameter, with the change in amplitude of the T-wave the

 next most sensitive parameter. The changes of P-R interval were the

 least sensitive.

 Table 18: Cardiovascular function and urinary chlordimeform in factory workers

 (personal communication by S.-Z. Xue, M. Wang, C.-M. Chu and X.-W.

 Zhou entitled "Effects of chlordimeform on cardiovascular function

 in humans with occupational exposure", 1993)

 Parameter measured Duration of continuous exposure (days)

 0 1 7 15 30

 Total urinary 0.000 0.311 0.627 0.642 0.773

 chlordimeform (mg/litre)

 Systolic BP (mmHg) 111/8.6a 105/7.7b 105/12c 102/10d 102/9.6c

 Diastolic BP (mmHg) 71/7.1 69/9.3 63/10c 65/8.2d 64/9.8d

 Heart rate (beat/min) 64.3/9.9 69.6/8.6d 67.2/6.5 70.0/9.4 71.4/12d

 Q-T interval (msec) 398/18.2 404/23.1 412/16.7d 418/22.3d 412/23.6d

 P-R interval (msec) 131/215 140/178d 140/212d 141/200a 143/317d

 a Figures are mean/standard deviation

 b P < 0.001

 c P < 0.01

 d P < 0.05

 The authors attributed major importance to the alteration in

 cardiovascular function in relation to chlordimeform intoxication, and

 in most cases considered cardiac failure to be the cause of death.

 Recognition of the effects on cardiac function may have been

 overlooked previously, firstly, because of the diversity of mild

 changes induced by chlordimeform and, secondly, because of the

 tendency to concentrate on the effects of the aniline-containing

 metabolites, such as methaema-globinaemia, haematuria, and

 haemorrhagic cystitis. A no-observed-effect-level (NOEL) of

 0.1 mg/litre of urinary chlordimeform plus 4-chloro- o-toluidine

 excretion is proposed as the threshold for effects on cardiovascular

 function following long-term, exposure while 0.3 mg/litre is proposed

 as the threshold for effects on cardiovascular function following

 short term exposure, even as short as one day. While the

 cardiovascular function parameters are unlikely to be useful as

 indicators of exposure, an understanding of the mechanism of action

 should assist in designing appropriate treatment.

 In a post-exposure surveillance programme, the chlordimeform-

 exposed group showed an increased prevalence of malignancy-associated

 surface markers on exfoliated urine cells, compared to geographical

 controls, but no tumours were found (Kenyon et al., 1993).

 8.2.3 Epidemiological studies

 8.2.3.1 4-Chloro- o-toluidine

 In a retrospective epidemiological study by Ott & Langner (1983)

 the mortality experience of 342 employees assigned to three aromatic

 amine-based dye production areas between 1914 and 1958 was examined in

 relation to duration of employment (<1 to 5 years) and interval since

 entry into these areas. 4-Chloro- o-toluidine represented one of a

 number of chemicals to which the workers were potentially exposed.

 4-Chloro- o-toluidine and two other aromatic amines ( o-toluidine

 and 4-chloro-acetyl- o-toluidine) to which the workers were exposed

 have been shown to be carcinogenic in animal studies. No deaths due to

 bladder cancer were observed, and no statistically significant

 increases in mortality by work area or duration of exposure within

 work area were found.

 In a retrospective study by Stasik (1988; 1991) of 116 workers

 occupationally exposed in Germany to 4-chloro- o-toluidine during

 manufacture prior to 1970, eight cases of bladder cancer, diagnosed

 between 1967 and 1985, were identified. This represents an incidence

 more than 70-fold higher than expected. Although occupational exposure

 to two other aromatic amines, o-toluidine and 6-chloro- o-

 toluidine, may have occurred, analysis of the production process

 indicated that exposure to 4-chloro- o-toluidine in the plant was

 considerably higher than exposure to these other two chemicals. The

 workers were exposed to relatively high levels (before 1970) for a

 median of 14 years. In two cases, however, the exposure period was

 only 1.5 and 4.0 years. No quantitative measurements of exposure were

 available. Two of the patients had suffered from haemorrhagic cystitis

 as a consequence of massive acute exposure to 4-chloro -o-toluidine

 at 4 and 14 years, respectively, before the tumour was diagnosed. The

 latency periods for these eight cases ranged from 17 to 38 years. The

 significantly increased incidence of bladder cancer in this study is

 remarkable.

 8.2.3.2 Chlordimeform

 An epidemiological study has been conducted on the incidence of

 cancer deaths of employees and their relatives on Xin-Yang Farm in

 Jiang-su Province of China (Gu et al., 1991). In this area,

 chlordimeform has been applied aerially in large amounts since 1974,

 in a relatively indiscriminate manner, with contamination of land,

 ponds, creeks, and gardens of adjacent houses. The study involved 7321

 people (3911 male, 3410 female and 1265 retired agricultural workers)

 over the period 1 January 1971 to 30 June 1987. During this period,

 there were 706 registered deaths (510 males, 196 females), of which

 198 were cancer deaths (160 males, 38 females). The standardized

 mortality ratio (SMR) was calculated on the basis of the specific

 mortality due to cancer in the adjacent Hai-men County. Many of the

 SMRs were significantly exceeded on the Xin-Yang Farm, as shown in

 Table 19. The incidences of bladder cancer adjusted to the national

 level were 2.65 (males) and 1.47 (females) per 100 000. The SMRs were

 260 (males) and 420 (females). During the period 1 July 1987 to

 30 June 1990, there were three more cases of bladder cancer (with one

 death) among the cohort members. The authors concluded there is

 evidence for an association between bladder cancer and exposure to

 chlordimeform, but that further data is needed to strengthen this

 association. It is noted that there was a high incidence of other

 tumour types in this study which makes the association between bladder

 cancer and exposure to chlordimeform more difficult to establish.

 Table 19. Standardized mortality ratio (SMR) for workers on the

 Xin-Yang farm (Gu et al., 1991)

 Cause of death Adjusted mortality Standardized mortality ratio

 (per 100 000) (95% C.I.)

 Male Female Male Female

 All deaths 785.1 610.0 134 (124-145) 139 (128-151)

 All cancers 214.0 130 113 (107-120) 128 (117-139)

 Oesophageal cancer 35.6 32.5 228 (208-249) 388 (352-428)

 Stomach cancer 61.4 24.5 175 (161-190) 120 (110-130)

 Liver cancer 31.6 6.9 40 (37-44) 27 (24-29)

 Colon cancer 8.8 6.5 133 (123-145) 79 (72-86)

 Lung cancer 34.2 16.9 135 (124-146) 147 (135-169)

 Leukemia 3.9 5.6 144 (133-157) 260 (235-285)

 Bladder cancer 4.1 3.0 197 (180-214) 750 (671-839)

 Breast cancer - 16.0 - 380 (345-419)

 Cervical cancer - 30.7 - 216 (198-234)

 Further epidemiological data on the association between cancer

 incidence and exposure to chlordimeform has been provided in papers by

 Xue et al. (1990; 1991). A summary of the findings of epidemio-logical

 studies between 1984 and 1988 is given in Table 20. Data from three

 counties and one farm are shown. The counties are located close to one

 another, with comparable environmental and socio-economic situations.

 The agricultural products are mainly rice and cotton. County A acted

 as a control, with little or no use of chlordimeform; County B was

 the largest user of chlordimeform; and County C started using

 chlordimeform at the earliest time. The results from the Xin-Yang farm

 are included for comparison. A comparison between the mortality rate

 in recent years (1984-1988) and the mortality rate in the years prior

 to the use of chlordimeform in these counties and Xin-Yang farm is

 shown in Table 21. There were excesses in the incidence of all deaths,

 deaths from cancer, and urinary bladder cancer for both sexes,

 although the data may not yet have reached the level of statistical

 significance.

 Table 21. Comparison of adjusted mortalities of urinary bladder

 cancer between 1984-1988 (county) and 1973-1975

 (prefecture) (Xue et al., 1990, 1991)

 Item County A County B County C Xin-Yang Farm /

 / Prefecture / Prefecture Prefecturea

 Male 1.52 / 1.10 0.77 / 0.77 1.12 2.65 / 1.02

 SRR 1.38 1.04 1.10 2.65b

 Female 0.41 / 0.35 0.46 / 0.17 0.55 1.47 / 0.35

 SRR 1.17 2.71b 1.57b 4.20b

 a The duration of observation was 1971-1987 (June 30)

 b p < 0.05

 In a retrospective study by Popp & Norpoth (1991) and Popp et al.

 (1992), the exposure and incidence of bladder cancer in a German

 chemical plant was examined. Chlordimeform was manufactured from

 4-chloro- o-toluidine and production commenced in December 1965.

 Production was not continuous, but rather was in response to orders,

 so workers were subject to different periods of exposure (generally

 8-12 weeks per year). Between 1965 and 1976, the exact levels of

 exposure were not available because measurement of the concentration

 in the air or monitoring of urine excretion was not carried out at

 that time. In 1976, production was ceased in order to improve working

 conditions and minimize human exposure. Production recommenced in 1980

 with improved containment and monitoring of urinary excretion of

 Table 20. Data on Epidemiological Studies with Chlordimeform during 1984-1988 (Xue et al., 1990, 1991)

 Items County A County B County C Xin-Yang Farm

 (control) (largest amount) (earliest in using)

 Year started using chlordimeform 1979 1977 1973 1973

 Population (annual average) 993 549 1 076 456 736 037 8732

 Average amount of chlordimeform 1.1 65.0b 29.8 89.2

 used (g/Mu/year)a

 All causes of mortality

 Male 584.5 675.7 761.0 785.1

 RR 1.2 (1.1-1.3) 1.3 (1.2-1.4) 1.3 (1.2-1.5)

 Female 438.1 891.7 668.5 625.9

 RR 2.0 (1.4-2.3) 1.5 (1.1-1.7) 1.4 (1.3-1.5)

 Cardiovascular mortalityc

 Male 143.2 167.7 221.6 -

 RR 1.2 (1.1-1.3) 1.6 (1.4-1.7)

 Female 138.2 280.2 234.8 -

 RR 2.0 (1.9-2.2) 1.7 (1.6-1.8)

 Respiratory mortalityc

 Male 99.6 100.4 127.2

 RR 1.0 (0.9-1.1) 1.3 (1.2-1.4)

 Female 82.1 145.1 124.0

 RR 1.8 (1.7-1.9) 1.5 (1.4-1.6)

 Table 20. (con't)

 Items County A County B County C Xin-Yang Farm

 (control) (largest amount) (earliest in using)

 All cancer mortalityc

 Male 188.5 246.6 232.2 214.9

 RR 1.3 (1.2-1.4) 1.2 (1.1-1.3) 1.1 (1.1-1.2)

 Female 101.7 227.1 145.5 130.0

 RR 2.3 (2.0-2.5) 1.4 (1.3-1.6) 1.3 (1.2-1.4)

 Bladder cancer mortalityc

 Male 2.08 (95)d 0.90 (26) 2.10 (32) 4.10 (4)

 RR 0.4 (0.39-0.47) 1.0 (0.9-1.2) 2.0 (1.8-2.2)

 Female 0.40 (15) 0.20 (9) 0.90 (14) 3.00 (2)

 RR 0.5 (0.46-0.55) 2.3 (2.1-2.5) 7.5 (6.7-8.4)

 a The Mu is a measure of area equivalent to 1/15th acre

 b Considered over the last 5 years

 c All mortality figures were age-adjusted

 d Figure in parentheses is the actual number of cases of bladder cancer

 workers. Production finally ceased in 1986. The company identified 170

 individuals who had come into contact with chlordimeform but many had

 minimal exposure. The number of workers involved in the production of

 chlordimeform was 49, and these comprised the study group. The period

 under investigation was from the year of employment to the end of

 1990. The expected incidence of bladder cancer (age- and sex-specific)

 was extracted from the cancer registers of Saarland (1988), the former

 German Democratic Republic (GDR) (1978-1982) and Denmark (1978-1982).

 The standard incidence rate (SIR) was the ratio of the number of cases

 observed to the expected number (see Table 22).

 Table 22. Standard incidence rates (SIRs) of bladder carcinoma in a

 group of 49 workers engaged in chlordimeform synthesis

 (Popp et al., 1992)

 Observed cases Expected number SIR 95% CI p value

 7 0.078 (GDR) 89.7 35.6 - 168.6 0.000002

 7 0.200 (Denmark) 35.0 13.9 - 65.7 0.00001

 7 0.130 (Saarland) 53.8 21.3 - 101.1 0.000005

 The average age for workers starting work was 30 (range 18-51), and

 the exposure ranged from 3 to 956 days. By the end of 1990, an average

 of 18 (10-25) years had passed since the start of exposure. Bladder

 cancer was detected in 7 of the 49 subjects by the end of 1990. Of the

 seven cases, six were diagnosed as transitional cell carcinoma and one

 as papillary carcinoma. In five cases, the exposure period could be

 determined, with an average of 575 days (range 291-766). The latency

 period was an average of 19 years (range 15-23), with an average age

 at diagnosis of 54 years (range 42-62). This study provides strong

 evidence of an association between exposure to 4-chloro- o-toluidine

 and human bladder cancer. All of the cases involved workers who were

 exposed to 4-chloro- o-toluidine while synthesizing chlordimeform

 before 1976. None of those workers who were handling the final

 product, chlordimeform, had developed bladder cancer by the end of

 1990.

 In a historical cohort study (personal communication by P. Boyle

 & G.J. Macfarlane to the IPCS, 1997), the bladder cancer incidence of

 847 men involved in the manufacture of chlordimeform in Australia,

 Switzerland, the United Kingdom and the USA was compared with that

 expected on the basis of population-based cancer registry rates.

 Subjects eligible to be included in the cohort were those who had been

 employed in the production or formulation of chlordimeform or who had

 otherwise been an integral part of a chlordimeform unit in a plant

 where it had been produced or formulated for at least 6 months. The

 results presented in Table 23 show an incidence rate of bladder cancer

 which was significantly higher than expected. Overall, ten cases were

 observed while 2.6 were expected. When the cohort was divided

 according to whether members had been exposed to chlordimeform and

 4-chloro- o-toluidine, or to chlordimeform alone, it was found that a

 significant excess of risk of bladder cancer also occurred in those

 workers thought not to have been exposed to 4-chloro- o-toluidine. In

 this group of 592 men, 5 cases of bladder cancer were observed, while

 1.4 cases were expected (SIR = 3.5, 95% CI (1.1, 8.3)). The authors

 concluded that despite the lack of information on potentially

 confounding factors in this study, the data indicated an association

 between excess risk of bladder cancer in this cohort and one or more

 aspects of the manufacture of chlordimeform.

 Table 23. Bladder cancer risk in a cohort of men exposed to

 chlordimeform (Boyle & Macfarlane, 1997)

 Plant location Cohort numbers Bladder cancer cases

 Observed Expected SIRa

 Switzerland 273 4 0.72 5.6

 USA (A)b 182 1 0.32 3.1

 United Kingdom 174 3 1.06 2.8

 USA (B)b 163 1 0.26 3.8

 Australia 55 1 0.27 3.7

 All plants 847 10 2.63 3.8

 95% CIc

 (1.8, 7.1)

 a Standardized Incidence Ratio

 b Different production sites

 c Confidence Interval

 9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

 9.1 Laboratory experiments

 9.1.1 Microorganisms

 There are no data on the effects of chlordimeform on

 microorganisms.

 9.1.2 Aquatic organisms

 9.1.2.1 Plants

 There are no data on the effects of chlordimeform on aquatic

 plants.

 9.1.2.2 Invertebrates

 There are no laboratory data on the effects of chlordimeform on

 aquatic invertebrates.

 9.1.2.3 Vertebrates

 The toxicity of chlordimeform to some species of fish has been

 determined (FAO/WHO, 1972; Mayer & Ellersieck, 1986), and is shown in

 Table 24.

 9.1.3 Terrestrial organisms

 9.1.3.1 Plants

 There are no data available for the effects of chlordimeform on

 plants.

 9.1.3.2 Invertebrates

 Dittrich (1966, 1967) first reported studies on the efficacy of

 chlordimeform as an acaricide with both ovicidal activity against

 insect eggs and adulticidal activity. It killed adult spider mites

 when applied as a vapour and as a spray, and penetrated plant tissues

 where it was released in ovicidal quantities. Since then, its efficacy

 as an insecticide has been studied in a wide range of species.

 Chlordimeform not only has a direct lethal action, particularly

 against eggs and early instar larvae of insects and acarines, but also

 has important sublethal effects, including sterilization of eggs,

 induction of hyperactivity, detachment of feeding ticks from hosts,

 Table 24. Toxicity of chlordimeform to fish

 Species Duration LC50 Reference

 (h) (mg/litre)

 Bluegill sunfish 24 1.0 FAO/WHO (1972)

 48 1.0

 96 1.0

 Trout 24 11.7 (8.73-15.8) FAO/WHO (1972)

 48 10.6 (7.80-14.50)

 96 7.14 (4.70-10.80)

 Cat fish 24 11.9 (8.98-15.9) FAO/WHO (1972)

 48 8.72 (6.26-21.1)

 96 4.54 (3.08-6.68)

 Rainbow trout 24 29 Mayer & Ellersiek

 96 13.2 (1986)

 Channel catfish 24 20.7 Mayer & Ellersiek

 96 20.2 (1986)

 Carp 24 65a FAO/WHO (1972)

 48 60a

 96 50a

 a Values are for TLm

 colony dispersal behaviour in ticks and mites, anti-feeding effects

 and disruption of mating and oviposition in Lepidoptera (Hollingworth,

 1976).

 Knowles & Shrivastava (1973) investigated its toxicity in house

 flies. The LD50 was 25 µg/fly, a dose which was not at a practical

 level for house-fly control, possibly due to the high rate of

 metabolism in this species. Pimley (1986) investigated the toxicity of

 chlordimeform to tsetse fly (Glossina morsitans). The median lethal

 dose was approximately 0.4 µg/fly for unfed tsetse, and 100% mortality

 was achieved with 2 µg/fly. Sublethal doses also caused a significant

 depression of feeding activity.

 The specificity of chlordimeform with regard to both eggs and

 larval stages was examined by Streibert & Dittrich (1977). Eggs of the

 three noctuid cotton pest moths, Heliothis armigera, Heliothis

 virescens, and Spodoptera littoralis, when exposed to a saturated

 atmosphere of 4 mg/m3, have very similar sensitivity to vaporized

 chlordimeform. Agrotis ipsilon, also a noctuid, on the other

 hand, is definitely less sensitive, and the coccinillid Epilachna

 varivestis was the most tolerant. The larval stages of all of these

 species were considerably less sensitive to chlordimeform vapour than

 the egg stage, but chlordimeform does seem to cause a decrease in the

 number of larvae in the field, possibly due to a repellent effect or a

 behavioural change rather than a direct toxic effect. These results

 with Spodoptera littoralis on the relative sensitivity of eggs and

 larvae were confirmed in the studies of Salvisberg et al. (1980).

 Davenport & Wright (1985) have also demonstrated the differential

 susceptibility of adult and larvae of the noctuid moths, Spodoptera

 littoralis and Heliothis virescens, and also highlighted the

 significantly higher toxicity of the hydrochloride salt, compared to

 the base, to the adults of both species.

 Sparks et al. (1993) studied the effects of several insecticides

 on ovicidal activity and alteration of octopamine titres in eggs of

 the tobacco budworm (Heliothis virescens). Chlordimeform was highly

 toxic to eggs of H. virescens. The authors reported that the

 alteration in the biogenic amine octopamine titres by chlordimeform

 might lead to a disruption in the ability of larvae to hatch from the

 egg.

 Crecelius & Knowles (1976) studied the sensitivity of the larvae

 of the cabbage looper, Trichoplusia ni, to the toxic effects of

 chlordimeform. Third instar larvae were more sensitive to the toxic

 effects of chlordimeform than the fifth instar larvae, possible due to

 slower penetration and slower metabolism of chlordimeform in the

 latter instar larvae.

 Bailey & Cathey (1985) demonstrated the effectiveness of

 chlordimeform in reducing the percentage egg hatch of Lygus

 lineolaris (Palisot de Beauvois) on pole bean ( Phaseolus

 vulgaris L.) pods and cotton ( Gossypium hirsutum L.). A solution

 of 0.09% chlordimeform, while not significantly reducing nymph

 emergence from eggs deposited on bean pole pods, did significantly

 reduce nymph emergence from eggs deposited on cotton plants.

 Salvisberg et al. (1980) also demonstrated that Spodoptera

 littoralis moths, when treated at doses as low as 10% of the LD50,

 showed symptoms of hyperexcitation, which resulted in abnormal

 patterns of egg-laying, a reduced number of eggs and lower fertility.

 Further studies by Davenport & Wright (1987) on Spodoptera

 littoralis have shown that chlordimeform hydrochloride significantly

 reduces food consumption in fifth-instar larvae when incorporated into

 the diet at a level of 0.1-10 mg/g or when topically applied. No

 mortality occurred during feeding, but mortality was increased during

 subsequent pupation and during emergence of the adult from the pupae.

 In adult moths, egg laying was significantly decreased when

 chlordimeform hydrochloride was applied topically (1 or 10 µg/moth).

 Further evidence that behavioural changes may be more important

 in reducing both the larval and insect populations following

 chlordimeform treatment has been provided by Shimizu & Fukami (1983)

 in studies of the larvae of the cabbage armyworm, Mamestra

 brassicae, which showed a prolonged period of wandering behaviour in

 the presence of chlordimeform. This may have caused a failure to find

 or prepare a suitable site for pupation.

 The behaviour-modifying effects of chlordimeform have also been

 studied by Blackwell (1988a,b; 1889) in the larvae of the large

 cabbage white butterfly, Pieris brassicae L. When placed on

 chlordimeform-dipped leaves, the larvae become excited, in contrast to

 their normal communal feeding behaviour. Locomotion was increased and

 feeding was significantly reduced as a result of disaggregation

 (Blackwell, 1988a). When applied directly to the larvae, chlordimeform

 caused excitation and inhibition of feeding (Blackwell, 1989). Direct

 application also caused developmental delays and mortality was

 increased at later developmental stages (Blackwell, 1988b).

 O'Brian et al. (1985) have studied the effect of insecticides on

 beneficial insects, and in particular, the effect of chlordimeform on

 the ecoparasitoid, Bracon mellitor, an important parasitoid of the

 boll weevil (Anthonomus grandis grandis). Chlordimeform was found to

 be more toxic to Bracon mellitor than to the boll weevil, and also

 reduced the number of egg deposited.

 The toxicity of chlordimeform hydrochloride to bees has been

 examined after both ingestion and contact. Ingestion of a 0.3%

 solution killed 18%, while ingestion of 0.15% killed approximately 7%.

 Contact with the same solutions did not increase the mortality rate

 (FAO/WHO, 1972). In a study by Johansen (1972), bees were exposed to

 field-weathered residues of a range of insecticides, including

 chlordimeform, on alfalfa foliage. Over a 24-h period, zero mortality

 was obtained with alfalfa leafcutter bees, alkali bees and honey bees

 exposed to 3-h-old residues.

 9.1.3.3 Vertebrates

 Fleming et al. (1985) examined the toxic and behavioural effects

 of chlordimeform on the game bird, the bobwhite quail (Colinus

 virginianus). When added to the diet of newborn chicks over a 7-day

 period, the lethal concentration to chicks was 2835 mg/kg diet

 (2169-3705 mg/kg diet). When chicks were fed a diet containing

 chlordime-form at a concentration of 1000 mg/kg diet for 7 days, they

 ate less, weighed less, travelled further from a fright stimulus in an

 avoidance test, and had a high locomotor activity in an open-field

 test than at lower dose levels. Chicks fed 100 or 1000 mg

 chlordimeform/kg diet scored more highly than controls in a visual

 cliff performance test. After a further 8 days on control diet, the

 chicks fed 1000 mg/kg diet still scored higher than controls on the

 avoidance test, but the open-field and cliff performance scores were

 similar to those of controls.

 In studies conducted on bobwhite quails and ducks, groups of

 animals (10 per treatment group, 30 per control group) were fed

 chlordimeform technical or chlordimeform 48% EC formulation in their

 diets for 5 consecutive days. The dose levels were 0, 10, 31.6, 100,

 316 or 1000 mg/kg diet. Both quails and ducks were tolerant of the

 presence of chlordimeform in the diet. With the technical material,

 one quail in each of the groups fed 100 and 316 mg/kg diet died,

 while, with the formulation, one quail in each of the groups fed 316

 and 1000 mg/kg diet died. All ducks survived treatment, even at the

 highest dose level (FAO/WHO, 1972).

 Hill et al. (1975) exposed three bird species, Japanese quail

 (Coturnix japonica), ring-necked pheasant (Phasianus colchicus)

 and mallard (Anas platyrhynchos), to chlordimeform. LC50 values for

 Japanese quail and ring-necked pheasant were determined to be 1749 and

 2608 mg/kg diet, respectively. The LC50 for mallard was determined to

 be >5000 mg/kg diet; only 20% mortality was reported at the highest

 exposure group, 5000 mg/kg diet. Hill & Camardese (1986) reported an

 LC50 of 5079 mg/kg diet for Japanese quail exposed to chlordimeform.

 9.2 Field Observations

 9.2.1 Microorganisms

 There are no field data on the effects of chlordimeform on

 microorganisms.

 9.2.2 Aquatic organisms

 There are no field data on the effects of chlordimeform on

 aquatic organisms.

 9.2.3 Terrestrial organisms

 9.2.3.1 Plants

 The possibility that some insecticides might enhance the growth

 of cotton plants has been suggested for some time. However, in the

 case of chlordimeform, debate has continued as to whether this effect

 is due to early season insect suppression (Bailey & Cathey, 1985) or

 to a physiological effect (Phillips et al., 1977). Cathey & Bailey

 (1987) have conducted controlled studies to examine the effects of

 multiple applications of chlordimeform on the growth and development

 of cotton ( Gossypium hirsutum L.) in both greenhouse and field

 studies. Plants were sprayed six times with chlordimeform either alone

 or in combination with fenvalerate at 5- to 7-day intervals, beginning

 at the six-leaf stage of plant development. In the absence of early

 season insects and when insect populations were maintained at a

 relatively low level, no increases in lint yield occurred on the

 chlordimeform-treated plants. However, yield increases did occur and

 insect populations became lower in these treated plots when early

 season insect populations in the test area were relatively high. None

 of the treatments influenced the boll components, boll size, seed

 index and lint percentage, or the first fibre properties, length,

 strength and micronaire.

 Field studies by Youngman et al. (1990) to determine the effects

 of several insecticides on growth, fruiting patterns and yield of the

 cotton plant, Gossypium hirsutum L., supported the conclusion that

 chlordimeform does not significantly increase any plant growth

 parameter when compared with the control.

 9.2.3.2 Invertebrates

 In a small field study conducted by Bull & House (1978), tests

 were conducted in 0.05-ha plots of cotton to compare lower and more

 frequent applications of chlordimeform with commercial mixtures of

 insecticides against natural populations of Heliothis species. The

 results indicated that the protection afforded was as good as with

 commercial mixtures, probably as a result of careful observation of

 the cotton to pinpoint the onset of significant egg production.

 In a another small field study by Wilson (1981), the potential of

 chlordimeform to control Heliothis species in cotton was tested

 separately or in combination with amitraz and the microbial

 insecticide, Bacillus thuringiensis. Chlordimeform was the most

 efficient of the three materials and controlled Heliothis species

 reasonably efficiently, but no control of the rough bollworm,

 Earias hueglei was obtained. There was also good control of the

 cotton looper, Anomis flava, and some indication of suppression of

 mites and aphids was obtained.

 The behaviour-modifying effects of chlordimeform have been

 demonstrated in field studies by Uk & Dittrich (1986) on the adult

 whitefly, Bemisia tabaci (Genn.), which attacks cotton in the Sudan.

 At dose levels of 500-2500 g chlordimeform/ha together with 960 g

 endosulfan/ha, there was evidence of irritation and mass emigration of

 adults from treated cotton foliage without detectable direct

 mortality.

 9.2.3.3 Vertebrates

 There are no field data on the effects of chlordimeform on

 vertebrates.

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

 10.1 Evaluation of human health risks

 10.1.1 Exposure

 Production and use of chlordimeform has now ceased worldwide

 and no further human exposure should occur. During the years of

 chlordimeform production and use, dietary and incidental exposure to

 chlordimeform occurred. Occupational exposure to chlordimeform and

 4-chloro- o-toluidine (used as a starting material for synthesis)

 occurred during manufacture and formulation, as well as during

 application. The major route of exposure was through dermal

 contamination. Application of chlordimeform occurred extensively by

 aerial spraying, but it was also applied by ground-rigs as well as by

 backpack spray equipment. Thus, agricultural workers were exposed

 during mixing, loading, washing, and flagging operations. General

 population exposure occurred through the consumption of food

 containing residues of chlordimeform, and to a lesser extent through

 by-stander exposure. In some cases, there was intentional ingestion of

 the formulation.

 Monitoring of urinary 4-chloro- o-toluidine has been found to be

 a useful indicator of exposure.

 10.1.2 Toxicity

 In both experimental animals and humans, there is extensive

 metabolism of chlordimeform, followed by rapid excretion via the

 urine. A major urinary metabolite is 4-chloro- o-toluidine. In

 experimental animals, symptoms of acute toxicity included neurotoxic

 as well as cardiovascular effects. There was no evidence of

 teratogenicity or reproductive effects. Following chronic

 administration, there was a dose-related increase in

 haemangioendotheliomas in mice. There was no treatment-related

 increase in tumour incidence in rats. Most of the mutagenicity studies

 with chlordimeform itself were negative, but there were sporadic

 reports of genotoxicity with 4-chloro- o-toluidine and to a more

 limited extent with N-formyl-4-chloro- o-toluidine.

 In humans, chlordimeform has been shown to have both acute and

 chronic effects. Acute poisoning caused fatigue, nausea and loss of

 appetite, and, in more severe cases, somnolence, cyanosis, urgency in

 urination, cystitis, cardiovascular effects (tachycardia, bradycardia,

 ECG changes), coma and shock. The significance of the cardiovascular

 effects in chlordimeform-induced mortality has only recently been

 recognized. While there have been fatalities as a result of acute

 chlordimeform exposure, in the majority of cases complete recovery

 occurs. Symptoms of chronic exposure include those of acute exposure

 as well as abdominal pain, skin itching and rashes, and gross or

 microscopic haematuria.

 With regard to carcinogenicity, the International Agency for

 Research on Cancer (IARC) has concluded that there is limited

 evidence in humans and sufficient evidence in experimental animals

 for the carcinogenicity of 4-chloro- o-toluidine. The available

 epidemiological data indicate an association between excess risk of

 bladder cancer and exposures entailed in the manufacture of

 chlordimeform. There is currently preliminary epidemiological evidence

 of an association between chlordimeform use and excess risk of bladder

 cancer.

 10.1.3 Risk evaluation

 With the withdrawal of the use of chlordimeform in agriculture

 and a cessation of production worldwide, there is no longer any risk

 associated with acute exposure except during the disposal of existing

 stocks. The risk associated with chronic exposure, however,

 particularly the risk of bladder cancer, will continue to be of

 concern for many years. Human bladder cancer has a long latency

 period, and establishing whether or not there is a link between

 chlordimeform exposure and bladder cancer will require continued

 health screening of significantly exposed individuals both from

 manufacturing plants and from those rural communities where

 chlordimeform was extensively used.

 10.2 Evaluation of effects on the environment

 Since chlordimeform is no longer used, no quantitative risk

 assessment for the environment has been performed. There are not

 expected to be any long-term detrimental effects on the environment as

 a result of past use of chlordimeform.

 11. CONCLUSIONS AND RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

 AND THE ENVIRONMENT

 11.1 Conclusions

 Chlordimeform has significant potential to cause both immediate

 and long-term toxicity in exposed individuals. Current information

 supports an association between an increased incidence of human

 bladder cancer and exposure to 4-chloro- o-toluidine, and, to a

 lesser extent, chlordimeform.

 Chlordimeform does not persist in the environment and therefore

 there are not expected to be any long-term detrimental effects on the

 environment as a result of past use.

 11.2 Recommendations for protection of human health and the

 environment

 Future commercial production or use of chlordimeform is not

 recommended. Existing stocks should be disposed of safely.

 Those with occupational exposure to chlordimeform should

 participate in a health screening programme that includes urinary

 cytology and the detection of haematuria.

 12. FURTHER RESEARCH

 The following studies are needed:

 1. epidemiological investigations on exposed populations.

 2. studies on the dose-response relationship between exposure to

 4-chloro- o-toluidine or chlordimeform and the induction of

 urinary bladder cancer in humans.

 13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

 Chlordimeform was considered by the International Agency for

 Research on Cancer (IARC) in 1983. IARC noted that no published study

 on the carcinogenicity of chlordimeform was available. However, it

 considered data on the carcinogenicity of 4-chloro- o-toluidine and

 concluded that the results of experiments on mice provided sufficient

 evidence that 4-chloro- o-toluidine, a metabolite of chlordimeform,

 is carcinogenic to experimental animals. No relevant data on humans

 were available. IARC concluded the available data were inadequate to

 evaluate the carcinogenicity of chlordimeform to humans (IARC, 1983).

 The carcinogenicity of 4-chloro- o-toluidine, the breakdown

 product and major metabolite of chlordimeform, was evaluated by IARC

 in 1990 (IARC, 1990). On the basis of the available published data, it

 was concluded that there is limited evidence in humans and

 sufficient evidence in experimental animals for the carcinogenicity

 of 4-chloro- o-toluidine. 4-chloro- o-toluidine and its strong acid

 salts were classified as probably carcinogenic to humans (Group 2A).

 Chlordimeform was considered at the 1971, 1975, 1978, 1979, 1980,

 1985 and 1987 FAO/WHO Joint Meeting on Pesticide Residues (JMPR). In

 1971, a temporary acceptable daily intake (ADI) for chlordimeform of

 0-0.01 mg/kg body weight was established, and temporary maximum

 residue levels (MRLs) were set for a number of crops and for the meat

 and milk of cattle (FAO/WHO, 1972). In 1975, the temporary ADI was

 maintained and some new temporary MRLs were established (FAO/WHO,

 1976). In 1978, the temporary ADI was reduced to 0-0.0001 mg/kg body

 weight, the temporary MRLs for all crops except cotton and cottonseed

 were withdrawn, and the MRLs for meat and milk of cattle were set at

 the level of detection (FAO/WHO, 1979). In 1979, 1980 and 1985, the

 temporary ADI of 0-0.0001 mg/kg body weight was extended (FAO/WHO,

 1980, 1981, 1986). In 1987, the temporary ADI for chlordimeform was

 withdrawn (FAO/WHO, 1988).

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 RÉSUMÉ

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

 Le chlordiméform est une base de force moyenne qui forme des sels

 stables avec les acides forts. A l'état pur, le chlordiméform et son

 chlorhydrate sont des solides cristallins incolores. Le point de

 fusion du chlordiméform base est de 32°C, celui du chlorhydrate étant

 de 225-227°C. La base est légèrement soluble dans l'eau (250 mg/litre)

 et facilement soluble dans les solvants organiques, tandis que le

 chlorhydrate est facilement soluble dans l'eau mais plus difficilement

 dans les solvants organiques. La tension de vapeur du chlordiméform

 est de 48 mPa à 20°C et son coefficient de partage entre l'eau et

 l'octanol (log Kow) est égal à 2,89. On peut faire appel à de

 nombreuses méthodes d'analyse pour la recherche et le dosage du

 chlordiméform dans les végétaux, le sol, l'eau et l'urine.

 2. Sources d'exposition humaine et environnementale

 Le chlordiméform n'existe pas à l'état naturel. On le prépare

 industriellement par condensation du réactif de Vilsmeier (obtenu par

 réaction du diméthylformamide sur POCl3, SOCl2 ou COCl2) soit avec

 la 4-chloro- o-toluidine, soit avec la l' o-toluidine, suivie d'une

 chloration du dérivé intermédiaire obtenu. On l'utilise comme

 acaricide à large spectre et il est principalement actif contre les

 formes mobiles des acariens et des tiques ainsi que contre les oeufs

 et les premiers stades de certains lépidoptères. Il agit en phase

 gazeuse aussi bien que par contact. Les premiers temps de son

 utilisation, on l'employait pour traiter des cultures très variées

 comme les fruits à pépins, les drupes, les choux et autres légumes,

 les raisins, le houblon, les agrumes, les cerises et les fraises. On

 l'utilise aussi en bains contre les tiques des bovins. Ces dernières

 années son usage s'est généralement limité au coton, mais on continue

 tout de même à l'utiliser sur le riz dans certains pays. Depuis

 1988/89 il n'est plus homologué dans la plupart des pays. En Chine, la

 production a cessé en 1992, de même que la vente en 1993.

 3. Transport, distribution et transformation dans l'environnement

 Bien que sa tension de vapeur ait une valeur moyenne, le

 chlordiméform ne s'évapore pas autant qu'on le penserait des surfaces

 végétales. Sa stabilité vis-à-vis de l'hydrolyse dépend fortement du

 pH; il est stable en milieu acide mais s'hydrolyse rapidement en

 milieu alcalin. Le chlordiméform est capable de s'adsorber sur les

 matières organiques dissoutes.

 Dans le sol, la disparition du chlordiméform est essentiellement

 imputable à l'action des microorganismes et, pour une moindre part, à

 l'hydrolyse chimique. Malgré la solubilité du composé dans l'eau, on

 ne trouve guère de traces de lessivage, ce qui peut s'expliquer par

 une adsorption aux matériaux argileux ou aux matières organiques du

 sol ainsi que par la biodégradation. Les principaux métabolites sont

 la N-formyl-4-chloro- o-toluidine et la 4-chloro- o-toluidine.

 Les plantes fixent le chlordiméform présent dans le sol en

 proportion faible mais mesurable et la concentration est suffisante

 pour affecter les ravageurs qui se nourrissent à leurs dépens. En

 traitement foliaire, la pénétration du chlordiméform dans la cuticule

 est limitée. Le chlordiméform est rapidement décomposé par les

 végétaux. Les principaux métabolites sont le déméthylchlordiméform, la

 N-formyl-4-chloro -o-toluidine et la 4-chloro -o-toluidine, cette

 dernière n'étant pas produite par toutes les plantes.

 Dans le sol, le chlordiméform et ses métabolites disparaissent

 selon une cinétique du premier ordre avec une demi-vie de 20 à 40

 jours.

 Les études de bioaccumulation montrent que les organismes

 aquatiques ne fixent qu'une petite quantité de chlordiméform et que

 celui-ci s'élimine rapidement une fois ces organismes replacés en eau

 pure.

 4. Concentrations dans l'environnement et exposition humaine

 On n'a pas procédé à des mesures de concentration dans l'air ou

 l'eau. Après traitement de rizières, on a retrouvé des résidus allant

 jusqu'à 2900 µg/kg dans les 5 premiers centimètres du sol et jusqu'à

 150 µg/kg dans les 5 centimètres suivants.

 On a fixé des teneurs limites en résidus pour un grand nombre de

 produits crus et dans certains cas, pour des préparations contenant

 ces produits. Les limites maximales de résidus fixées par le Codex ont

 été supprimées.

 Il y a eu des cas d'exposition au chlordiméform au cours de la

 préparation, de la formulation et de l'épandage de ce produit. Depuis

 quelques années, on utilise la concentration urinaire totale du

 chlordiméform et de ses métabolites pour surveiller l'exposition et il

 y a d'ailleurs une bonne corrélation entre cette concentration et le

 degré de contamination cutanée. Dans les industries cotonnières où

 l'on a soumis les ouvriers agricoles à une surveillance générale de la

 concentration urinaire en chlordiméform, on a constaté que les plus

 exposés étaient les chargeurs, les laveurs et les mécaniciens et les

 moins exposés les signaleurs et les pilotes.

 5. Cinétique et métabolisme chez les animaux de laboratoire et

 l'Homme

 Chez les mammifères, le chlordiméform est facilement résorbé au

 niveau des voies digestives ainsi que par la voie transcutanée. Il est

 ensuite rapidement excrété à raison de 80% environ dans l'urine et de

 10-15% dans les matières fécales. De petites quantités de résidus sont

 présentes au bout de 10 jours dans tous les tissus mais rien n'indique

 qu'il y ait bioaccumulation. Après application cutanée chez l'Homme,

 on constate également une excrétion urinaire rapide.

 On retrouve dans l'urine plusieurs métabolites du chlordiméform

 sous forme oxydée et conjuguée, à savoir principalement la

 N-formyl-4-chloro- o-toluidine, et la 4-chloro- o-toluidine.

 In vitro, on retrouve les mêmes métabolites, mais avec prédominance

 de la 4-chloro- o-toluidine.

 6. Effets sur les mammifères de laboratoire et les systèmes d'épreuve

 in vitro

 Les épreuves pratiquées sur un certain nombre d'espèces montrent

 que la chlordiméform présente une toxicité aiguë modérée par la voie

 orale et la voie transcutanée. Chez le rat, les principaux métabolites

 sont peu toxiques par voie orale. Chez le lapin, le chlordiméform ne

 provoque qu'une légère irritation oculaire et cutanée. Après

 exposition de courte ou de brève durée au chlordiméform ou à ses

 métabolites, on peut observer, au niveau des constantes

 hématologiques, des modifications qui sont imputables au traitement et

 on constate, à dose élevée, certains signes qui dénotent une

 hyperplasie de l'épithélium des canaux biliaires et de la vessie. Il

 n'y pas d'accroissement de la fréquence des tumeurs chez le rat. Chez

 la souris, on observe, après administration par voie alimentaire de

 chlordiméform, de N-formyl-4-chloro -o-toluidine ou de

 4-chloro- o-toluidine, une augmentation, liée à la dose, des tumeurs

 malignes hémorragiques d'origine vasculaire appartenant à la classe

 des hémangio-endothéliomes, dont la présence entraîne un accroissement

 de la mortalité parallèle à la dose.

 Le chlordiméform n'a pas d'effet indésirable sur les différents

 aspects de la fonction de reproduction et il n'a aucun pouvoir

 tératogène.

 Le chlordiméform a fait l'objet d'un grand nombre d'épreuves de

 génotoxicité in vitro et in vivo. Aucune d'elles n'a donné de

 résultat positif, étant entendu qu'il s'agissait de la matière active

 et non de formulations. Par ailleurs, un certain nombre d'observations

 sporadiques non confirmées font état d'une activité mutagène induite

 par la N-formyl-4-chloro- o-toluidine et par la 4-chloro- o-

 toluidine. Il n'existe qu'une seule description de transformations

 cellulaires provoquées par le chlordiméform et par la 4-chloro -o-

 toluidine. Chez des souris et des rats traités par le chlordiméform,

 on a constaté une que le composé se liait à l'ADN des cellules

 hépatiques. A dose beaucoup plus élevée, il se forme chez les mêmes

 animaux un important adduit hydrophobe.

 Le chlordiméform provoque des effets pharmacologiques et

 biochimiques divers chez l'animal, et notamment des effets

 cardiovasculaires, une hypothermie, une hyperexcitabilité, une

 modification des fonctions visuelle et auditive ainsi que la

 modulation des amines biogenèse et des enzymes pharmacométabolisantes.

 7. Effets sur l'Homme

 Les intoxications aiguës se traduisent par une fatigue, des

 nausées et une perte d'appétit, avec, dans les cas graves, somnolence,

 cyanose, besoin impérieux d'uriner, cystite, effets cardiovasculaires

 (tachy-cardie, bradycardie, anomalies de l'ECG), coma et état de choc.

 En général, la récupération est totale.

 Après une exposition de longue durée au chlordiméform, on peut

 observer encore d'autres symptômes tels que des douleurs abdominales,

 des démangeaisons et des éruptions (en cas d'exposition cutanée)

 accompagnés d'une hématurie macroscopique ou micro-scopique. On a

 signalé de nombreux cas d'intoxication présentant des symptômes

 d'exposition de longue durée parmi les ouvriers d'unités de production

 de chlordiméform et des ouvriers agricoles.

 Les données épidémiologiques obtenues à la suite de cas

 d'exposition professionnelle montrent qu'il existe une forte

 corrélation entre l'exposition à la 4-chloro -o-toluidine et le

 cancer de la vessie. En revanche, on n'a guère obtenu d'éléments qui

 militeraient en faveur d'une association entre ce type de cancer et

 l'exposition au chlordiméform.

 8. Effets sur les autres êtres vivants au laboratoire et dans leur

 milieu naturel

 Après épandage de chlordiméform sur le sol, on n'a pas observé

 d'effets sensibles sur les populations de champignons, de bactéries ou

 d'actinomycètes terricoles.

 Il n'existe pas de données toxicologiques de laboratoire

 concernant les invertébrés dulçaquicoles. En présence de

 chlordiméform, il y a inhibition de la croissance des larves

 d'huîtres, avec une CE50 de 5,7 mg/litre. Pour la crevette rose,

 le seul crustacé étudié, la CL50 à 96 h a été trouvée égale à

 7,1 mg/litre et des valeurs allant de 1 à 54 mg/litre ont été obtenues

 pour le même paramètre chez les poissons. On ne possède aucune donnée

 relative à la toxicité chronique pour les espèces aquatiques.

 L'ensemble des résultats de laboratoire et des données recueillies sur

 le terrain indique que le composé est toxique pour de nombreux

 arthropodes terrestres non visés.

 Chez l'abeille, la toxicité de contact se traduit par une DL50

 de 120 µg/g, la toxicité par voie orale correspondant à une valeur de

 187 µg/g. Trois heures après l'épandage de chlordiméform sur de la

 luzerne, l'exposition de certaines espèces d'abeilles aux résidus

 encore présents sur les plantes, n'a provoqué aucune mortalité.

 La CL50 par voie alimentaire varie de >1000 à > 5000/kg de

 nourriture pour diverses espèces d'oiseaux.

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

 l'environnement

 On a observé des signes d'intoxication aiguë chez des

 travailleurs qui, peut-être par suite de l'inobservation des mesures

 de sécurité, avaient été fortement exposés à du chlordiméform au cours

 de la préparation ou de l'utilisation de ce produit. Comme, à ce qu'il

 semble, il n'est plus produit ni utilisé nulle part dans le monde, il

 ne devrait plus y avoir de cas d'intoxication aiguë. Le risque lié à

 une exposition chronique et en particulier, le risque de cancer de la

 vessie, subsistera cependant pendant de nombreuses années. Il faut

 continuer à effectuer des contrôles sanitaires chez les sujets qui ont

 subi une exposition notable pour avoir travaillé dans des ateliers de

 production de chlordiméform ou avoir vécu dans des zones rurales où le

 produit était largement utilisé.

 Comme il s'agit d'un produit qui n'est plus en usage, on n'a pas

 procédé à une évaluation quantitative du risque qu'il représente pour

 l'environnement. On ne pense pas que celui-ci puisse subir des effets

 nocifs à long terme qui soient attribuables à l'utilisation antérieure

 du produit.

 10. Conclusions et recommandations

 Il existe un risque non négligeable que le chlordiméform produise

 des effets toxiques immédiats ou à plus long terme chez les individus

 exposés. Les données disponibles accréditent l'idée d'une association

 entre l'augmentation de l'incidence du cancer de la vessie chez

 l'homme et l'exposition à la 4-chloro- o-toluidine et, dans une

 moindre mesure, au chlordiméform.

 Le chlordiméform ne persiste pas dans l'environnement et il ne

 devrait donc pas y avoir d'effets nocifs à long terme sur celui-ci qui

 résulteraient de l'usage antérieur du composé.

 Il n'est pas recommandé de reprendre la production ou l'usage du

 chlordiméform dans un but commercial. Les stocks existants doivent

 être éliminés selon les règles de sécurité.

 Les personnes exposées au chlordiméform de par leur profession

 doivent être soumises à des examens cytologiques vésicaux et à une

 recherche systématique de l'hématurie dans le cadre d'un programme

 général de dépistage.

 RESUMEN

 1. Identidad, propiedades físicas y químicas y métodos analíticos

 El clordimeformo es una base de fuerza media que forma sales

 estables con ácidos fuertes. Tanto el clordimeformo como su sal

 hidroclorada en estado puro son sólidos cristalinos incoloros. El

 punto de fusión del clordimeformo (base) es de 32°C, mientras que el

 de la sal hidroclorada es de 225-227°C. El clordimeformo (base) es

 poco soluble en agua (250 mg/litro) y fácilmente soluble en

 disolventes orgánicos, mientras que la sal hidroclorada es fácilmente

 soluble en agua pero menos soluble en disolventes orgánicos. El

 clordimeformo (base) tiene una presión de vapor de 48 mPa a 20°C y un

 log Kow de 2,89. Se dispone de una amplia gama de métodos analíticos

 para detectar y cuantificar la presencia de clordimeformo en las

 plantas, el suelo, el agua y la orina.

 2. Fuentes de exposición humana y ambiental

 El clordimeformo no existe en la naturaleza. Se produce

 comercialmente mediante condensación del reactivo de Vilsmeier

 (obtenido por reacción de la dimetilformamida con POCl3, SOCl2

 o COCl2) con 4-cloro- o-toluidina o bien con o-toluidina y

 cloración ulterior del producto intermedio resultante. Se ha utilizado

 como acaricida de amplio espectro y actúa principalmente contra las

 formas móviles de ácaros y garrapatas, así como contra los huevos y

 las crisálidas en estado inicial de algunos insectos del orden

 Lepidóptera. Es activo en la fase de vapor, así como por contacto.

 Cuando comenzó a utilizarse, se aplicaba a productos de una amplia

 variedad de cultivos, tales como frutas de pipas, frutas de hueso,

 berzas, hortalizas, uvas, lúpulo, cítricos, manzanas, peras, cerezas y

 fresas. También se utilizaba en baños antiparasitarios para combatir

 las garrapatas del ganado. En los últimos años, su uso se limitaba por

 lo general al algodón, aunque en algunos países se seguía aplicando al

 arroz. En la mayoría de los países, su registro se abandonó

 voluntariamente en 1988/1989. En China dejó de producirse en 1992 y de

 venderse en 1993.

 3. Transporte, distribución y transformación en el medio ambiente

 El clordimeformo tiene una presión de vapor moderada pero su

 evaporación de la superficie de las plantas es inferior a la que

 cabría prever. La estabilidad hidrolítica del clordimeformo depende

 mucho del pH; es estable en condiciones ácidas pero se hidroliza

 rápidamente en condiciones alcalinas. El clordimeformo tiene un

 potencial de adsorción a la materia orgánica disuelta.

 Hay dispersión del clordimeformo en el suelo, principalmente por

 acción microbiana y, en menor medida, por hidrólisis química. Pese a

 la solubilidad del clordimeformo en agua, hay pocos indicios de

 lixiviación, lo que puede deberse a su adsorción a minerales

 arcillosos y a la materia orgánica del suelo, así como a su

 biodegradación. Los principales metabolitos son la N-formil-

 4-cloro- o-toluidina y la 4-cloro- o-toluidina.

 La absorción del clordimeformo por las plantas a partir del suelo

 es escasa pero detectable, y suficiente para afectar a las plagas que

 se alimentan de ellas. El clordimeformo aplicado a las hojas sólo

 tiene una capacidad limitada de penetrar en las capas cuticulares. El

 clordimeformo se degrada rápidamente en las plantas. Sus principales

 metabolitos son el demetilclordimeformo, la N-formil-4-cloro-

 o-toluidina y la 4-cloro- o-toluidina, aunque no todas las plantas

 estudiadas produjeron 4-cloro- o-toluidina.

 El clordimeformo y sus metabolitos se dispersan en el suelo

 conforme a una cinética de primer orden, con una semivida de 20-40

 días.

 Los estudios sobre bioacumulación indican una escasa absorción

 del clordimeformo por los organismos acuáticos y una rápida depuración

 de éstos después de haber sido transferidos a un agua limpia.

 4. Niveles medioambientales y exposición humana

 No se han medido los niveles de clordimeformo en el aire ni en el

 agua. Tras la aplicación de clordimeformo a unos arrozales, en el

 suelo se hallaron residuos en concentraciones de hasta 2900 µg/kg en

 los 5 cm primeros de profundidad, y de 150 µg/kg en los 5 cm

 siguientes.

 Se establecieron niveles máximos de residuos aplicables a una

 amplia variedad de productos sin elaborar y, en algunos casos, de

 residuos trasladados a los alimentos elaborados. Los límites máximos

 aplicables a los residuos de clordimeformo se han retirado del Codex

 Alimentarius.

 Había exposición ocupacional al clordimeformo durante la

 fabricación, la formulación y la aplicación del producto. En los

 últimos años la exposición se ha vigilado mediante la determinación de

 los niveles totales de clordimeformo y de sus metabolitos presentes en

 la orina, y hay una correlación positiva entre el nivel en la orina y

 el grado de contaminación cutánea. Entre los trabajadores agrícolas de

 los algodonales sometidos a una amplia vigilancia de la excreción

 urinaria de clordimeformo, los niveles más altos de exposición se

 hallaban en los cargadores, lavadores y mecánicos, y los niveles más

 bajos en los obreros señalizadores y pilotos.

 5. Cinética y metabolismo en animales de laboratorio y en el ser

 humano

 Los mamíferos absorben fácilmente el clordimeformo por el tracto

 gastrointestinal y a través de la piel. Lo excretan rápidamente,

 alrededor del 80% por la orina y del 10-15% por las heces. Al cabo de

 unos 10 días se observan niveles bajos de residuos en todos los

 tejidos y no hay indicios de bioacumulación. Tras la administración

 cutánea a seres humanos, se observa una excreción rápida semejante por

 la orina.

 Varios metabolitos oxidados y conjugados del clordimeformo se

 excretan por la orina; los principales son el demetilclordimeformo, la

 N-formil-4-cloro- o-toluidina y la 4-cloro- o-toluidina. En

 estudios in vitro se han observado los mismos metabolitos, siendo el

 principal la 4-cloro- o-toluidina.

 6. Efectos en mamíferos de laboratorio y en sistemas de pruebas

 in vitro

 En ensayos realizados en varias especies, el clordimeformo

 administrado por vía oral y cutánea ha mostrado tener una toxicidad

 aguda moderada. Los principales metabolitos han mostrado tener una

 toxicidad oral baja en ensayos realizados en ratas. El clordimeformo

 provoca solamente una ligera irritación cutánea y ocular en el conejo.

 Tras una exposición breve o prolongada de ratones y ratas al

 clordimeformo o a sus metabolitos pueden observarse cambios asociados

 al tratamiento en los parámetros hematológicos y, con dosis elevadas,

 indicios de hiperplasia del epitelio de las vías biliares y de la

 vejiga. El clordimeformo no aumenta la incidencia de tumores en las

 ratas. En los ratones, después de administrar a través de la dieta

 clordimeformo N-formil-4-cloro- o-toluidina o 4-cloro- o-

 toluidina, se observa, de forma relacionada con la dosis, un aumento

 de los tumores malignos hemorrágicos de origen vascular clasificados

 como hemangioendoteliomas malignos, que producen un aumento de la

 mortalidad asociado con la dosis.

 El clordimeformo no afecta a los parámetros reproductivos ni

 tiene potencial teratogénico.

 Se ha ensayado el clordimeformo en una amplia variedad de pruebas

 de genotoxicidad in vitro e in vivo. No se han comunicado

 reacciones positivas a ninguna de esas pruebas, en las que se ensayó

 clordimeformo en estado puro. Además, se han comunicado varios

 informes esporádicos y no confirmados de actividad mutagénica inducida

 por la N-formil-4-cloro- o-toluidina y la 4-cloro- o-toluidina. Un

 informe describe una inducción de la transformación celular por efecto

 tanto del clordimeformo como de la 4-cloro- o-toluidina. En el hígado

 de los ratones y las ratas expuestos se producen enlaces con el ADN.

 Se ha observado un importante aducto hidrofóbico, en los ratones en

 niveles mucho mayores que en las ratas.

 El clordimeformo induce diversos efectos farmacológicos y

 bioquímicos en los animales, tales como cambios cardiovasculares,

 hipotermia, hiperexcitabilidad, efectos sobre las funciones visual

 central y auditiva y modulación de las aminas biogénicas y de las

 enzimas que metabolizan fármacos.

 7. Efectos en el ser humano

 La intoxicación aguda causa fatiga, náuseas, pérdida del apetito

 y, en casos más graves, somnolencia, cianosis, micción imperiosa,

 cistitis, efectos cardiovasculares (taquicardia, bradicardia,

 alteraciones del ECG), coma y choque. En general se produce una

 recuperación completa de la intoxicación aguda.

 Otros síntomas asociados a la exposición crónica al

 clordime-formo son dolores abdominales, prurito y exantemas

 (exposición cutánea), así como hematuria macroscópica y microscópica.

 Se ha comunicado un gran número de casos con síntomas clínicos de

 exposición crónica tanto entre los obreros de las plantas de

 producción de clordimeformo como entre los trabajadores agrícolas.

 Los indicios epidemiológicos relacionados con la exposición

 ocupacional muestran una fuerte asociación entre la exposición al

 metabolito 4-cloro- o-toluidina y la incidencia de cáncer de vejiga

 en el ser humano. Actualmente se dispone de pocos indicios de

 asocia-ción entre la exposición al clordimeformo y el cáncer de vejiga

 en el ser humano.

 8. Efectos en otros organismos en el laboratorio y en el medio

 ambiente

 No se observaron efectos significativos en poblaciones de hongos

 de la tierra, bacterias o actinomicetos tras la aplicación de

 clordime-formo al suelo.

 No existen datos de laboratorio sobre la toxicidad en los

 invertebrados de agua dulce. El clordimeformo inhibió el crecimiento

 de larvas de ostras, con una CE50 de 5,7 mg/litro. La CL50 a las

 96-h para los camarones rosados, único crustáceo estudiado, fue de

 7,1 mg/litro y los valores de la CL50 a las 96-h para los peces

 oscilaron entre 1 y 54 mg/litro. No se dispone de datos sobre

 toxicidad acuática crónica. La combinación de datos obtenidos en el

 laboratorio y sobre el terreno revela que el clordimeformo es tóxico

 para una amplia gama de artrópodos terrestres no combatidos.

 Con respecto a las abejas, se ha comunicado una DL50 de

 toxicidad por contacto de 120 µg/g y una DL50 de toxicidad oral de

 187 µg/g. No se produjo mortalidad sobre el terreno tras la exposición

 de especies de abejas a los residuos presentes en la alfalfa tres

 horas después del rociado.

 La CL50 en la dieta de varias especies de pájaros osciló entre

 >1000 y >5000 mg/kg de dieta.

 9. Evaluación de los riesgos para la salud humana y efectos en el

 medio ambiente

 La exposición intensa durante la producción o la utilización,

 debida posiblemente a la insuficiencia de las medidas de seguridad,

 dio lugar a síntomas de intoxicación aguda en los trabajadores. Como

 se ha notificado que se ha suspendido la producción y la utilización

 de clordimeformo en todo el mundo, no deberían producirse nuevos casos

 de intoxicación aguda. Sin embargo, el riesgo asociado a la exposición

 crónica, en particular el riesgo de cáncer de vejiga, seguirá siendo

 preocupante durante muchos años. Debería proseguir el reconoci-miento

 médico de las personas que han estado muy expuestas en las plantas de

 producción y en las comunidades rurales donde se haya aplicado

 extensamente el clordimeformo.

 Dado que el clordimeformo ha dejado de utilizarse, no se ha

 realizado ninguna evaluación cuantitativa de los riesgos para el medio

 ambiente. A largo plazo no se prevén efectos perjudiciales para el

 medio ambiente como consecuencia de la utilización de clordime-formo

 en el pasado.

 10. Conclusiones y recomendaciones

 El clordimeformo tiene un potencial significativo para causar

 tanto toxicidad inmediata como a largo plazo en las personas

 expuestas. La información de que se dispone actualmente apunta a una

 asociación entre una mayor incidencia de cáncer de vejiga en el ser

 humano y la exposición a la 4-cloro- o-toluidina y, en menor medida,

 al clordimeformo.

 El clordimeformo no persiste en el medio ambiente, por lo que a

 largo plazo no se prevén efectos perjudiciales como consecuencia de su

 utilización en el pasado.

 Se recomienda que el clordimeformo no se produzca comercialmente

 ni se utilice en el futuro. Las reservas existentes deberían

 eliminarse sin correr riesgos.

 Las personas expuestas profesionalmente al clordimeformo deberían

 participar en un programa de reconocimiento médico que comprenda

 citología urinaria y detección de hematuria.

 See Also:

 [Toxicological Abbreviations](http://www.inchem.org/documents/eintro/eintro/abreviat.htm)

 [Chlordimeform (ICSC)](http://www.inchem.org/documents/icsc/icsc/eics0124.htm)

 [Chlordimeform (WHO Pesticide Residues Series 1)](http://www.inchem.org/documents/jmpr/jmpmono/v071pr02.htm)

 [Chlordimeform (WHO Pesticide Residues Series 5)](http://www.inchem.org/documents/jmpr/jmpmono/v075pr09.htm)

 [Chlordimeform (Pesticide residues in food: 1978 evaluations)](http://www.inchem.org/documents/jmpr/jmpmono/v078pr07.htm)

 [Chlordimeform (Pesticide residues in food: 1979 evaluations)](http://www.inchem.org/documents/jmpr/jmpmono/v079pr12.htm)

 [Chlordimeform (Pesticide residues in food: 1980 evaluations)](http://www.inchem.org/documents/jmpr/jmpmono/v080pr07.htm)

 [Chlordimeform (Pesticide residues in food: 1985 evaluations Part II Toxicology)](http://www.inchem.org/documents/jmpr/jmpmono/v85pr04.htm)

 [Chlordimeform (Pesticide residues in food: 1987 evaluations Part II Toxicology)](http://www.inchem.org/documents/jmpr/jmpmono/v87pr05.htm)

 [Chlordimeform (IARC Summary & Evaluation, Volume 30, 1983)](http://www.inchem.org/documents/iarc/vol30/chlordimeform.html)