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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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

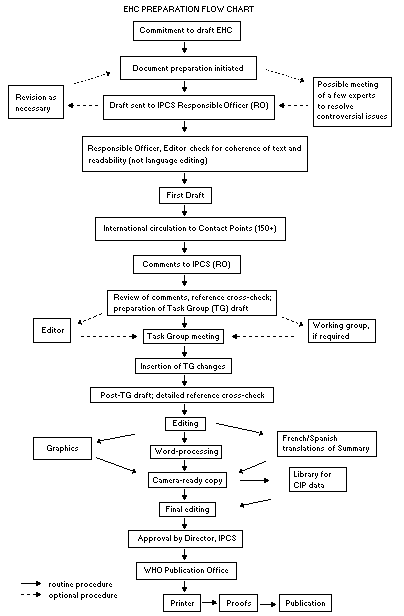
document, it then goes for language editing, reference checking, and

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.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR CHLORDIMEFORM

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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 STRUCTURE 1

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-

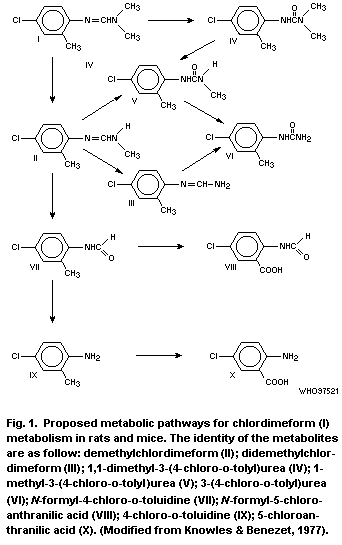
chloro- o-toluidine. Incubation of extracted bile with enzymes or

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).

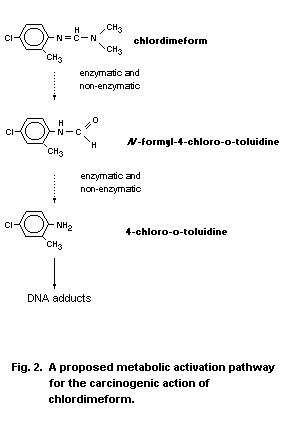
Taken together, the evidence strongly implicates 4-chloro- o-

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)