WHO Pesticide Residues Series, No. 1

1971 Evaluations of some pesticide residues in food

World Health Organization
Geneva, 1972

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1971 EVALUATIONS OF SOME PESTICIDE RESIDUES IN FOOD

THE MONOGRAPHS

The evaluations contained in these monographs were prepared by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues that met in Geneva from 22 to 29 November 1971.[1]

World Health Organization
Geneva
1972

[1] Pesticide Residues in Food: Report of the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, Wld Hlth Org. techn. Rep. Ser., No. 502; FAO Agricultural Studies, 1972, No. 88.

These monographs are also issued by the Food and Agriculture Organization of the United Nations, Rome, as document AGP-1971/M/9/1.

Since 1961, the Food and Agriculture Organization of the United Nations and the World Health Organization have been holding joint meetings of experts to discuss the hazard to the consumer arising from pesticide residues in food and feedstuffs. The meetings have been held annually since 1965. For some pesticides it has been possible to establish acceptable daily intakes. These, together with relevant agricultural data, have been used as a basis for recommending maximum permitted concentrations of the residues in foods. These maximum concentrations are listed as " tolerances " where the residues result from recommended usage of a pesticide. Where the residues occur as a result of circumstances not designed to protect the food against pest attack, such concentrations are listed as " practical residue limits ". In appropriate cases, the meetings have also recommended methods of analysis for pesticide residues.

Each meeting results in the publication of a report, which sets out certain general principles and summarizes the conclusions reached and the recommendations made. In addition, the evaluations, acceptable daily intakes, and tolerances for pesticide residues in food, together with information on the identity of the pesticides considered by the meeting, are issued in the form of monographs. The reports are published both in the *WHO Technical Report Series* and in the series *FAO Agricultural Studies*. The monographs are available in the *WHO Pesticide Residues Series* and as FAO documents.

WHO publications may be ordered, direct or through booksellers, from the addresses shown on the back cover of this volume.

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* Addendum.

INTRODUCTION

A Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues was held in Geneva in November 1971. The general considerations, including the principles adopted for the evaluations and a summary of the results of evaluations on a number of pesticide residues, appear in the publication, "Report of the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues".[1] Additional information, including previously unpublished summaries of data considered by the Joint Meeting in arriving at recommendations for acceptable daily intakes, tolerances and methods of analysis, is to be found in this publication.

Many of the compounds considered at this meeting have been previously evaluated in earlier publications. If only a limited amount of additional information on these compounds has become available in the intervening years, only this latter information is summarized in the pertinent monograph, and reference is made to the previously published evaluation, which should also be consulted by the reader who wishes to obtain a complete evaluation of the compound. Such monograph addenda are indicated by an asterisk in the "Contents", p. iii. If a large amount of data has become available since the previously published evaluation, or if the compound was first considered by the Joint Meeting in 1971, the pertinent monograph is reproduced in its entirety.

As much relevant information as possible has been included in the monographs. This has been obtained from the published literature wherever possible, but other sources of information have also been used. Early and complete publication of the results of research in this field is very important, particularly of that part which could form the basis for estimation of acceptable daily intakes and appropriate tolerances.

Publication allows the research to be scrutinized and criticized by scientists from disciplines not necessarily represented at the meeting. Data contained in unpublished reports, because they may include more detail than published work, are often acceptable. However, such reports must be complete and non-confidential and indicate authorship.

Five annexes are included at the end of this series of monographs. Annex I is a reproduction of Annex I in the Report of the 1971 Joint Meeting, and is a summary of recommendations concerning acceptable daily intakes, tolerances and practical residue limits as of December 1971. Annex II gives relevant FAO/WHO publications

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[1] Pesticide residues in food. Report of the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Group on Pesticide Residues, Wld Hlth Org. techn. Rep. Ser., No. 502; FAO Agricultural Studies, No. 88.

concerning the source of all the previous monographs of various compounds. Annex III comprises amendments and additions to definitions of terms, which were included in the Report of the 1971 Joint Meeting. Annex IV - Fumigants. Annex V lists the membership of the 1971 Joint Meeting of the FAO Working Party of Experts and WHO Expert Committee on Pesticide Residues.

NOTE TO THE READER

Any comments on evaluation for acceptable daily intakes should be addressed to:

Food Additives Unit
World Health Organization
Geneva, Switzerland

Any comments on residues in food and their evaluation should be addressed to:

Plant Protection Service
Plant Production and Protection Division
Food and Agriculture Organization
Rome, Italy

CHLORDIMEFORM

IDENTITY

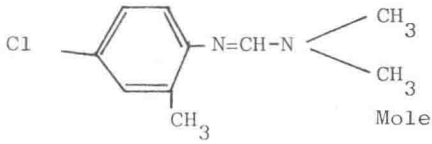
Chemical name

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

Synonyms

Chlorphenamidine, C-8514, Schering 36,268, SN 36 268.
Galecron ®, Acaron ®, Fundal ®, Spike ®.

Structural formula



Molecular weight 196.7

Other information on identity and properties

Clordimeform is used as a free base or as its hydrochloride salt. Physical properties of both base and hydrochloride salt are given below.

	Chlordimeform base	Chlordimeform hydrochloride
Melting point	32°C	225-227°C
Vapour pressure (20°)	3.5×10^{-4} Torr	2.2×10^{-7} Torr
Solubility in water	250 ppm	>50%
chloroform	>20%	1-2%
hexane	>20%	0.1%

Chlordimeform base is applied as an emulsifiable solution while the hydrochloride is used as a water-soluble powder.

Technical chlordimeform hydrochloride has a purity of a least 96%. The major impurities are 2, methyl-4-chlorformamidine, 4-chloro-o-toluidine-hydrochloride and sodium chloride.

Chlordimeform is rather stable in strong acids. It is readily hydrolyzed, however, in weakly-acid to weakly alkaline solutions. Its half-life in water containing 5% of methanol was determined to be 42 hours at pH 7 (30°C) and five hours at pH 9 (30°C) respectively.

EVALUATION FOR ACCEPTABLE DAILY INTAKE

Biochemical aspects

Table I shows the potential metabolites for chlordimeform.

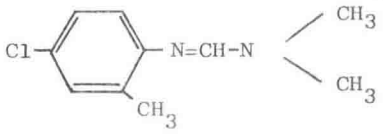
Four 120 g male rats treated orally with 270 µg of phenyl H^3-labelled (tritiated) chlordimeform secreted 19.74 to 23.03% of the dose in bile over a 24-hour period. Groups of four 130 g female rats similarly treated eliminated 52.8% (range 41.8-59.6%) and 2.5% (range 0.13-5.30%) in urine and faeces respectively in 24 hours. A pair of rats observed for 14 hours eliminated 66.2, and 64.9% administered H^3 label in urine, and 11.4 and 14.9% administered H^3 label in faeces. Twenty-four hour elimination following intravenous injection of 270 µg phenyl H^3-labelled chlordimeform in rat comprised 53.7% (range 52.0-55.6%) and 1.42% (range 1.19-1.84%) administered H^3, in urine and faeces respectively (Gerhards and Kolb, 1966).

The urine from a male rat collected over 72 hours subsequent to oral administration of 1.1 mg H^3-labelled chlordimeform contained 49% of the administered H^3 label. Free extractables comprised 22% of the H^3 label, 10% was in the water phase and 17% was reactive to form extractable glucuronides. The free extractable H^3 label comprised chlordimeform, 4-chloro-o-toluidine (IV), N-formyl-4-chloro-o-toluidine (III), N'-(4-chloro-o-tolyl)-N-methyl-formamidine (II). Glucuronides were based on the same compounds found as free extractables. The author notes that identified compounds may be formed after secretion of the urine (Gerhards, 1967).

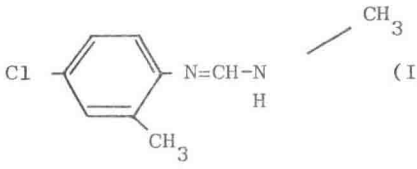
Single oral dosing of groups of three 120 g male rats with 270 µg phenyl H^3-labelled chlordimeform resulted in residues of administered H^3 label (expressed as percentage of dose/g of tissue) in liver (0.29%), kidney (0.22%) and lymph nodes (0.13%) after eight hours. After 24 hours, 0.35% and 0.13% of administered H^3 were present per g of tissue in gastrointestinal tract (and content) and liver respectively. All other tissues contained less than 0.1% H^3 label/g at eight hours, and less than 0.06% H^3 label at 24 hours. Twenty-four hour urine and faeces contained 57.5 and 3.9% of the total administered H^3 label respectively compared with 46.4% and 4.3% from rats sacrificed at eight hours (Gerhards and Kolb, 1966).

Three 120 g male rats were intubated with 270 ug phenyl H^3-labelled chlordimeform for seven consecutive days. Fifty-nine per cent. and 10% of the administered H^3 label were voided in urine and faeces respectively during the dosing period. Tissue residues at the termination of dosing were less than 0.03% of the administered H^3 label (Gerhards and Kolb, 1966).

TABLE I. POTENTIAL TRANSFORMATION PRODUCTS OF CHLORDIMEFORM

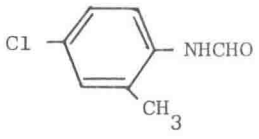


(I) N'-(4-chloro-o-tolyl)-N,N-dimethylformamidine (chlordimeform)

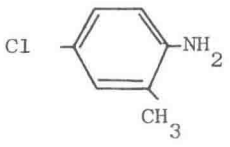


(II) N'-(4-chloro-o-tolyl)-N-methylformamidine

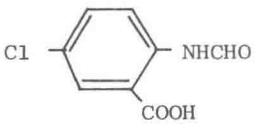
desmethyl chlordimeform



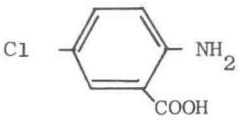
(III) N-formyl-4-chloro-o-toluidine



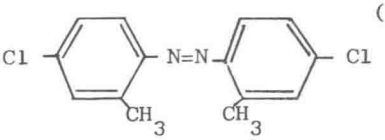
(IV) 4-chloro-o-toluidine



(V) N-formyl-5-chloroanthranilic acid



(VI) 5-chloroanthranilic acid



(VII) 2,2'-dimethyl-4,4'-dichloroazobenzene

Pairs of male and female rats were treated orally with 3 μCi of C^{14}-tolyl labelled chlordimeform. A similar group received C^{14} methyl labelled 4-chloro-o-toluidine (IV). Urine and faeces were collected at 3, 12, 24, 48 and 72 hours after dosing. Urinary and faecal elimination of C^{14} label after 72 hours comprised 88% and 7.5% of the administered dose of chlordimeform-C^{14}, and 71% and 24.5% of the administered 4-chloro-o-toluidine-C^{14}. Chloroform extraction removed 30% of the radioactivity from the urine of chlordimeform-C^{14} treated rats, the extract containing chlordimeform, N'-(4-chloro-o-tolyl)-N-methylformamidine (II), N-formyl-4-chloro-o-toluidine (III), and 4-chloro-o-toluidine (IV), in addition to three unidentified metabolites. A considerable amount of radioactivity remained at the point of origin of the chromatograph, the amount remaining increasing with time, (30% at three hours and 75% at 72 hours). At three hours, the four identified compounds were present in approximately equal amounts. By 12 hours the level of N'-(4-chloro-o-tolyl)-N-methylformamidine (II) had decreased to approximately 25% of the level of any of the other three compounds. By 48 hours, chlordimeform levels were half those of the other two compounds, and by 72 hours, N-formyl-4-chloro-o-toluidine (III) was present in the greatest proportion. At sacrifice (72 hours), tissue levels based upon C^{14} levels were 0.21 ppm in liver, 0.15 ppm in muscle, 0.11 ppm in fat and less than 0.1 ppm in other tissues. Metabolites in ethyl acetate-extracted urine from rats given C^{14} labelled 4-chloro-o-toluidine (IV) comprised 5-chloroanthranilic acid (VI) and N-formyl-5-chloroanthranilic acid (V). The proportion of unmetabolized 4-chloro-o-toluidine (IV) decreased with time whilst that of N-formyl-5-chloroanthranilic acid (V) increased. The level of 5-chloroanthranilic (VI) acid remained constant. A large amount (20-50%) of the radioactivity remained at the origin of the chromatograph. Five unidentified compounds were noted. Tissue levels based upon C^{14} levels at 72 hours after dosing were 0.33 ppm in fat, 0.26 ppm in liver, 0.2 ppm in kidney and oviduct, 0.1 ppm in brain, and less than 0.1 ppm in other tissues (Knowles and Sen Gupta, 1970).

Two female dogs (18 and 20 kg) were given a single oral dose of 10 μCi chlordimeform C^{14}, and a single male dog (12 kg) which had undergone cannulation of the gall-bladder and ligation of the bile duct was given 20 μCi chlordimeform C^{14} orally. Urine was collected (by catheterization) at 1, 3, 6, 12, 24, 48 and 72 hours. Faeces were collected at similar time intervals. Of the administered C^{14} 85% was recovered in urine, 0.6% in faeces, and 5% in the bile by 72 hours. 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 (II) and 4-chloro-o-toluidine (IV) in about equal quantities, but about four times as much N-formyl-4-chloro-o-toluidine III) at one hour after treatment. The level of unchanged chlordimeform and N'-(4-chloro-o-tolyl)-N-methylformamidine (II) decreased steadily with time, whereas 4-chloro-o-toluidine (IV) and N-formyl-4-chloro-o-toluidine (III) rose to maximum levels between

six and 12 hours 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 (VI), N-formyl-5-chloroanthranilic acid (V) and three unidentified compounds were present. Some radioactivity still remained at the origin. The urinary C^{14} not extracted by chloroform was treated with enzymes (β-glucuronidase, β-glucuronidase-aryl sulfatase) to form "aglycones". About 75% of the remaining C^{14} 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 (III). In addition, more of one of the unidentified metabolites was present. Again re-chromatography of the 45% radioactivity remaining at the origin with more polar solvents revealed 5-chloroanthranilic acid (VI) to be the major product. In the bile, peak concentration of radioactivity occurred at eight hours. About 10% of this activity could be partitioned into ether, and thin-layer chromatography of the extract indicated the same four compounds seen in urine chloroform extract. N'-(4-chloro-o-tolyl)-N-methylformamidine (II), N-formyl-4-chloro-o-toluidine (III) and an unidentified compound accounted for most of the activity at two hours. By six hours, 75% of the activity was due to N-formyl-4-chloro-o-toluidine (III). Incubation of extracted bile with enzyme or acid gave the same "aglycone" compounds as found in urine. Tissue residues of C^{14} at 72 hours ranged from 72 ppb in liver through kidney (30 ppb), lung (13.5 ppb), spleen and brain (11.9 ppb), heart and fat to pancreas at 5 ppb (Sen Gupta and Knowles, 1970).

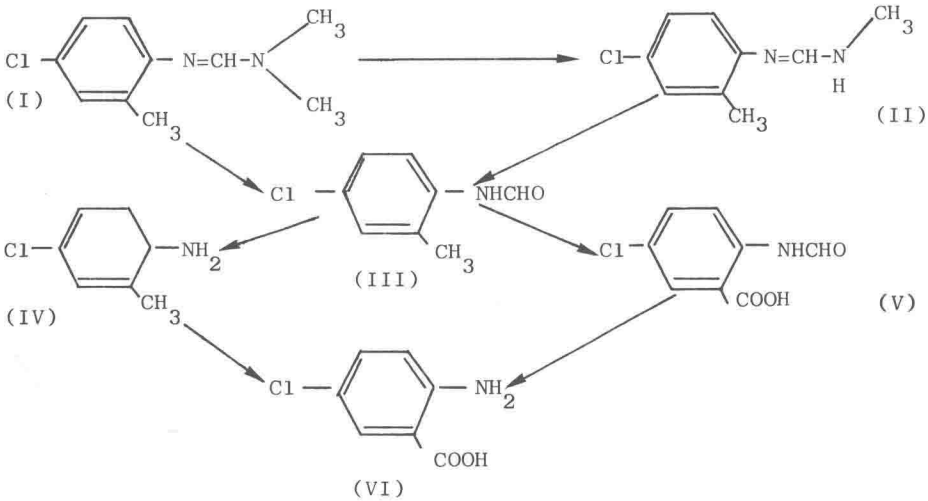
Incubation of chlordimeform (H^3 labelled) for 120 minutes with rat liver homogenate resulted in 24% unchanged chlordimeform, 45% 4-chloro-o-toluidine, and 11% unidentified metabolites being formed. Rabbit liver homogenate yielded 53%, 40% and 7% respectively (Gerhards & Kolb, 1966). The rat liver homogenate studies were confirmed using C^{14} labelled chlordimeform. In addition, chlordimeform degradation was shown to require the presence of nicotinamide. Three unidentified metabolites were also observed. No azo-derivatives were detected. Spleen homogenates were inactive with regard to chlordimeform degradation (Rose, 1969a).

Further in vitro studies have shown that plant peroxidases can result in the production of symmetrical azo-derivatives from 4-chloro-o-toluidine. Animal catalases do not result in formation of azo-derivatives (see below) (Rose, 1969b).

Incubation of 60 µg H^3-labelled chlordimeform (30 µCi) with 5 ml human plasma yielded N-formyl-4-chloro-o-toluidine only. Conversion was 25% in five hours, and 50% in 20 hours (Gerhards and Kolb, 1966).

A number of experiments were conducted by Ciba Ltd (1969c, d) to verify the presence or absence of azobenzene formation from chlordimeform or 4-chloro-o-toluidine in mammalian tissues. In the first series 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, catalyzes 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 series of experiments it was demonstrated that rat liver and spleen homogenates, which were fortified with nicotinamide, and which degraded chlordimeform to N-desmethyl-chlordimeform (II) and small quantities of N-formyl-4-chloro-o-toluidine (III) and 4-chloro-o-toluidine (IV) 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.

Chlordimeform degradation has been shown to proceed according to the following pathways (Knowles, 1970):



See also "Fate of Residues. In Animals".

TOXICOLOGICAL STUDIES

Special studies

(a) Pharmacological studies

Chlordimeform hydrochloride was administered at graded doses of 0.01, 0.1, 1.0, 10 and 100 mg to the isolated perfused rabbit heart, the organ being challenged with norepinephrine before and

after dosing. Contractile force was substantially decreased by 1.0 mg. Effect on coronary flow and cardiac rate was less marked. Higher doses temporarily stopped heart contractions. Guinea-pig isolated ileum was exposed to graded doses of 1.0, 3.2, 10, 32, 100 and 320 µg/ml of chlordimeform hydrochloride and evaluated for its effect on acetylcholine, serotonin, histamine and barium induced contractions. Bath concentrations of 3.2 µg/ml inhibited histamine contractions by about 50% concentrations of 320 µg/ml were required to induce a similar effect on acetylcholine, serotonin, and barium induced contractions. In the intact dog, effect of graded doses of 1, 3, 10, 30 or 100 mg/kg chlordimeform hydrochloride on blood pressure, cardiac rate, respiration, vasomotor response to epinephrine, acetylcholine, histamine, tyramine, DMPP, carotid occlusion and peripheral vagal stimulation were evaluated. Chlordimeform hydrochloride exerted a hypotensive effect and caused increased respiration. A dose of 100 mg/kg was lethal. Vasomotor response to tyramine was enhanced, whereas the pressor response to carotid occlusion was blocked (Teeters and Blackmore, 1968).

(b) Reproduction studies

Rat. Four groups of 10 male and 20 female rats were fed 0, 100, 250 and 500 ppm chlordimeform in corn oil via the diet during three parental, and three two-litter filial generations. Parental bodyweight prior to mating tended to be reduced in all test groups, especially at 500 ppm. The same tendency was apparent with regard to food consumption. Fertility index, gestation index, live birth index, sex ratio, mean litter size, and birth weight of pups were comparable to controls in all generations. At 500 ppm, lactation index was reduced in F1a, F1b and F3a litters. Weaning weight of offspring was depressed in all 500 ppm litters. Gross pathological examinations on parents and pups dying during the study, and on 10 male and 10 female weanlings of the F3b generation revealed no compound related effects (Blackmore, 1969a).

Rabbit. Three groups of 10 impregnated female New Zealand white rabbits (the day of impregnation being considered as day 0 of gestation) were intubated on days 8 through 16 of gestation with 0, 7.5 or 30 mg chlordimeform/kg/day. Five rabbits per group were sacrificed on day 28 of gestation. Parental mortality, abortion rate, corpora lutea to implantation ratio, litter size, incidence of resorptions, stillbirths, foetal weight, foetal length, and incidence of skeletal, and tissue abnormalities were unaffected by the test compound. In rabbits littering normally, gestation length, litter size and litter weights were normal (Blackmore, 1969b).

(c) Studies on metabolites

Oral LD_{50} determinations in male and female rats.

Compound	Duration of observation (days)	LD_{50} (mg/kg)	References
N'-(4-chloro-o-tolyl)-N-methylformamidine	14	150	Sachsse and Bathe, 1971a
N-formyl-4-chloro-o-toluidine	14	2900	" " " 1970a
4-chloro-o-toluidine (base)	7	cal000	" " " 1971c
4-chloro-o-toluidine - HCl	14	860	" " " 1970d
Phenamidine (base)	7	cal500	" " " 1971d
Phenamidine - HCl	14	860	" " " 1970f
o-chlordimeform (base)	7	300-400	" " " 1971f
o-chlordimeform - HCl	14	540	" " " 1970h
Dichlordimeform (base)	7	ca900	" " " 1971h
Dichlordimeform - HCl	14	260	" " " 1971j

Dermal LD_{50} determinations in male and female rats (24 hours occluded exposure).

Compound	Duration of observation (days)	LD_{50} (mg/kg)	References
N'-(4-chloro-o-tolyl)-N-methylformamidine	14	>2150	Sachsse and Bathe, 1971b
N-formyl-4-chloro-o-toluidine	14	>2150	" " " 1970b
4-chloro-o-toluidine (base)	7	cal800	" " " 1971c
4-chloro-o-toluidine - HCl	14	>2150	" " " 1970e
Phenamidine (base)	7	cal800	" " " 1971e
Phenamidine - HCl	14	>2150	" " " 1970g
o-chlordimeform (base)	7	ca300	" " " 1971g
o-chlordimeform - HCl	14	800	" " " 1970i
Dichlordimeform (base)	7	ca950	" " " 1971i
Dichlordimeform - HCl	14	>2150	" " " 1970k

Acute toxicity

ACUTE TOXICITY OF CHLORDIMEFORM BASE

Animal	Route	Sex	LD_{50} (mg/kg)	References
Mouse	i.p.	Mixed	110	Sachsse and Ullman, 1970
Rat	Oral	Male	178	Weir, 1968
Rat	Oral	Female	460	Weir, 1968
Rat	Oral	Male	220	Mastri et al., 1969
Rat	Oral	Female	170	Mastri et al., 1969
Dog	Oral	Female	ca100	Weir, 1967
Dog	Oral	Male	ca150	Hurni and Sachsse, 1969a
Dog	Oral	Female	ca400	Hurni and Sachsse, 1969a
Rat	Dermal	Mixed	640	Sachsse and Bathe, 19701
Rat	Inhalation*	Mixed	17 400 mg/m^3	Sachsse and Ullman, 1971

* Inhalation exposure was for one hour.

Hypoactivity, dyspnoea, muscular weakness, tremours, straub tail, spasms and convulsions preceded death following oral administration. Dyspnoea, exophthalmus, prostration, spasms and convulsions preceded death following dermal application. No local skin irritation occurred. No pathological changes were noted in rat following oral treatment, although pale or blotchy livers, pale kidneys, and haemorrhagic intestinal contents were observed after dermal treatment. In the dog, oral administration resulted in congestion of liver, kidneys, and lungs (the lungs also being oedomatous and haemorrhagic).

ACUTE TOXICITY OF CHLORDIMEFORM HYDROCHLORIDE

Animal	Route	Sex	LD_{50} (mg/kg)	References
Mouse	Oral	Mixed	220	Gunzel and Richter, 1967
Rat	i.v.	Male	95	Tripod, 1967
Rat	s.c.	Male	130	Tripod, 1967
Rat	Oral	Mixed	265	Gunzel and Richter, 1965
Rat	Oral	Mixed	355	Gunzel and Richter, 1965

ACUTE TOXICITY OF CHLORDIMEFORM HYDROCHLORIDE (continued)

Animal	Route	Sex	LD_{50} (mg/kg)	References
Rat	Oral	Male	305	Tripod, 1967
Rat	Oral	Male	325	Mastri et al., 1969
Rat	Oral	Female	330	Mastri et al., 1969
Rat	Dermal		ca4000	Gunzel and Richter, 1966a
Rabbit	Dermal		> 4000	Gunzel and Richter, 1966b
Rat	Inhalation*		> 5.8 g/m^3	Sachsse and Ullman, undated

* Inhalation exposure was for one hour.

Symptoms were similar to those for the base.

ACUTE TOXICITY OF CHLORDIMEFORM FORMULATIONS

Animal	Route	Sex	Formulation	LD_{50} (mg/kg)	References
Mouse	Oral	Male	EC 50	320	Aohi and Meda, 1966
Mouse	Oral	Female	50 s.p.	752	Shionogi C, undated
Rat	Oral	Mixed	EC 50	610	Hurni and Sachsse, 1969b
Rat	Dermal	Mixed	EC 50	2100	Sachsse and Bathe, 1971j
Rat	Dermal	Mixed	50 s.p.	>3000	Hurni and Sachsse, 1969c
Rat	Oral	Mixed	50 s.p.	1100	Gunzel and Richter, 1969
Dog	Oral	Mixed	50 s.p.	400	Gunzel and Richter, 1968

A suicide victim ingested 30 ml of Galecron® EC 50 formulation. Upon admission to hospital, an unknown time after drinking chlordimeform solution, the patient was comatosed; and respiration and heartbeat had ceased. The latter was restored by massage and adrenaline injection. A respirator was used but death occurred within 24 hours. No autopsy was performed (Oda, 1969).

Short-term studies

Rat. Four groups of 10 male and 10 female rats were intubated six times weekly for one month with 0.5 ml/100 g body-weight of 2% CMC, containing chlordimeform base at concentrations such as to give dose levels of 0, 25, 50 or 100 mg/kg/dose. Body-weight was markedly reduced in both sexes at 100 mg/kg/dose. Hyperexcitability