

HANDBOOK of TOXICOLOGY

Volume V
Fungicides

NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL

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Foreword

The Handbook of Toxicology, Volume V, Fungicides, is the ninth of a continuing series of publications*, each containing information, chiefly tabular, in one or more of the biological sciences. This book was prepared under Aero-Medical Laboratory Contract No. AF 33(616)-2873 between the National Academy of Sciences-National Research Council and the Wright Air Development Center. The contract is administered under the direction of the Aero-Medical Directorate of Laboratories, Wright Air Development Center, Edward F. Westlake, Major USAF, Project Monitor, Project No. 7165--"Health Hazards of Air Force Materials and Radiation." The work was carried out under the direction of the Committee on the Handbook of Biological Data, operating under the Division of Biology and Agriculture of the National Academy of Sciences-National Research Council.

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Handbook of Toxicology, Vol. I, Acute Toxicities	1955
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Handbook of Respiration	1958
Handbook of Toxicology, Vol. III, Insecticides	1959
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Introduction

The term "fungicide," as herein used, includes any substance that destroys fungi, or inhibits their growth or reproduction. As befitting this series of Handbooks, selection of such substances for inclusion in Volume V was determined by the toxicological information available. A list of some 500 additional compounds with bibliographic references appears in Appendix II.

For the most part, compounds are presented according to the nomenclature of Chemical Abstracts. Deviation from this procedure occurs in the case of recent name changes, i.e., Fungicidin to Nystatin, with Fungicidin now the alternative name. For easy reference, the latter is included in the Index, as are all the more common alternative names for each compound.

Patent numbers, United States and foreign, are contained in Appendix I. Of the 196 compounds comprising this book, 112 are represented there.

With the exception of the structural formulas which were calculated from the Periodic Chart of the Elements, THE MERCK INDEX, Ed. 6, 1952 (Merck & Co., Inc., Rahway, N. J.), information for this volume has been gathered from the records of the Committee on Control of Deterioration and the Chemical-Biological Coordination Center of the National Academy of Sciences-National Research Council, as well as from the literature and from unpublished reports of experimental work on fungicides. A simple code (bracketed numbers) has been employed to indicate data source, with the full reference given in the Bibliography. So far as possible, literature citations conform to the LIST OF ABBREVIATIONS FOR SERIAL PUBLICATIONS, Fourth Series, 1948, Army Medical Library, Washington, D. C. (U. S. Government Printing Office), and the 1955 SUPPLEMENT thereto.

The material contained in this handbook has been examined for accuracy by the analysts and has also been reviewed by authorities in the field of pathology. It must be emphasized, however, that the data, particularly those concerned with toxicity, are not precise and should be interpreted only as indications of activity. This book is offered not as a definitive work, but as the preliminary structure for a more exhaustive and better-documented report. Corrections, suggestions, and additions would therefore be welcomed.

Abbreviations

Bibliographic

CBCC = Chemical-Biological Coordination Center
NAS = National Academy of Sciences
NIH = National Institutes of Health
NRC = National Research Council
PDC = Prevention of Deterioration Center

Dose

ED = effective dose
LC = lethal concentration
LD = lethal dose
ED₅₀ = dose effective in 50% of an experimental group of organisms
LC₅₀ } = concentration or dose lethal for 50% of a group of organisms
LD₅₀ }
MED = minimum effective dose
MLD = minimum lethal dose
MTD = maximum tolerated dose

Route of Administration

c.t. = cutaneous	p.o. = oral
i.m. = intramuscular	r.t. = rectal
i.p. = intraperitoneal	s.c. = subcutaneous
i.v. = intravenous	s.t. = stomach tube

Measurement

da = day	g = gram
hr = hour	kg = kilogram
min = minute	mg = milligram
cc = cubic centimeter	μg = microgram
L = liter	M = mole
ml = milliliter	ppm = parts per million

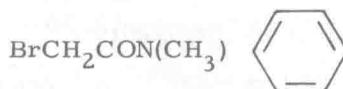
Fungicides

1. ACETANILIDE, 2-BROMO-N-METHYL-

ALTERNATIVE NAME (Bromoacetyl)methylaminobenzene.

MOLECULAR FORMULA $C_9H_{10}BrNO$

STRUCTURAL FORMULA



PHYSICAL AND CHEMICAL PROPERTIES Colorless prisms. Molecular weight, 227.984. Melting point, 48°C. Soluble, approximately 1:2, in acetone, benzene; "Cellosolve," approximately 1:4. Stable at room temperature. [48]

TESTS In vitro. Growth of inoculum (approximately 7.5×10^3 spores placed on treated slide for germination test) inhibited: Botrytis cinerea Fr., (0.65 $\mu g/sq\ cm$) 98-100%; Sclerotinia fructigena Aderh. and Ruhl., (0.65 $\mu g/sq\ cm$) 93-97%; Alternaria brassicae (Berk.) Sacc., (0.2-0.65 $\mu g/sq\ cm$) 0-50%. [49]

Growth of inoculum (1/8-inch, mycelial-covered cotton thread, rolled in 10% test compound in inert base of waterproof limestone powder) inhibited: Corticium solani (Prill. and Delacr.) Bourd. and Galz., Botrytis cinerea Fr., Fusarium nivale Auct., F. caeruleum (Lib.) Sacc., 98-100%; Helminthosporium avenae Eidam., 0-50%. [49]

TOXICITY LD₅₀ in mice, approximately 60 mg/kg, p.o., in acacia. Skin irritation. [48]

USE Protectant of materiel.

2. ACETIC ACID, DICHLORO-

ALTERNATIVE NAMES Dichloroethanoic acid; 2,2-Dichloroacetic acid; Dichloroacetic acid; Urner's liquid.

MOLECULAR FORMULA $C_2H_2Cl_2O_2$

STRUCTURAL FORMULA $Cl_2CHCOOH$

2. ACETIC ACID, DICHLORO- (Concluded)

PHYSICAL AND CHEMICAL PROPERTIES Colorless liquid. Pungent odor. [192]
Molecular weight, 128.950. Melting point, -4°C . Boiling point, $193\text{--}194^{\circ}\text{C}$. Specific gravity, 1.5724 (13°C). [53] Soluble at 25°C in acetone, benzene, carbon tetrachloride, ether. Also soluble in water, alcohol, n-heptane, methanol. [118]

TESTS In vitro.

	$\mu\text{g/sq cm}$	% Inhibited
<u>Stemphylium sarcinaeforme</u> Cav.	1000	100
	100	41
	10	6
	1	0
<u>Sclerotinia fructicola</u> (Wint.) Rehm.	1000	93
	100	11
	10	0

[8]

Chaetomium globosum, and Aspergillus niger (Van Tiegham): 1% of test compound prevented infestation [64].

TOXICITY

Animal	LD ₅₀ , mg/kg	Route	Time of Death
Mouse	5520(3810-8000)	p.o.	36 hr
Rabbit	510(390-670)	c.t.	
Rat	4480(4290-4690)	p.o.	36 hr

[120]

COMPARATIVE TOXICOLOGY LD₅₀ for dosage by mouth is of the same order of magnitude as the LD₅₀ for acetic acid [250].

USE Medicinal.

3. ACETOPHENONE, p-AMINO-

ALTERNATIVE NAME p-Aminophenyl methyl ketone.

MOLECULAR FORMULA $\text{C}_8\text{H}_9\text{NO}$

STRUCTURAL FORMULA



PHYSICAL AND CHEMICAL PROPERTIES Yellow needles. Molecular weight, 135.160. Melting point, 106°C [118], 110°C (corr.) [228]. Boiling point, 205°C [118], $293\text{--}295^{\circ}\text{C}$ [228]. Soluble in aqueous alcohol, boiling ether, boiling water. Slightly soluble in benzene, petroleum, ether. [228]

3. ACETOPHENONE, p-AMINO- (Concluded)

TESTS In vitro. Aspergillus niger (Van Tiegham): 1 drop of spore suspension and 250 ppm of test compound in nutrient-toxic-agar, incubated 96 hours at 30°C. Growth inhibited 69%. [229]

TOXICITY LD₅₀ in mice, 465 ± 19 mg/kg, i.p. [120]. In male mice given i.p. injection of test compound dissolved in water or propylene glycol, 10 out of 10 survived 200 mg/kg, 1 out of 8 died after 300 mg/kg, 8 out of 8 after 400 mg/kg; observation period, 10 days. [280]

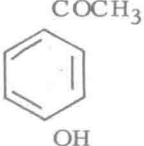
USE Protectant of materiel.

4. ACETOPHENONE, 4'-HYDROXY-

ALTERNATIVE NAME p-Hydroxyacetophenone.

MOLECULAR FORMULA C₈H₈O₂

STRUCTURAL FORMULA


O=Cc1ccc(O)cc1

PHYSICAL AND CHEMICAL PROPERTIES Solid. Molecular weight, 136.144. Melting point, 103°C [69], 109°C [153]. Boiling point, 147-148°C (3 mm Hg). Specific gravity, 1.109 [153]. Soluble at 25°C in water, acetone, carbon tetrachloride, methanol, benzene, ether, VMP naphtha [69]. Very soluble in alcohol [153].

TESTS In vitro. Spores of Stemphylium sarcinaeforme Cav., and Monilinia fructicola: ED₅₀, 1000 µg/sq cm. [138]

In vivo. Phomopsis citri and Diplodia natalensis (stem-end rot in citrus fruit): 25 ethylene gas treated oranges dipped in 5% solution of test compound, dried, and stored at 70°F for 3 weeks. Decay prevented; no rind injury. [294]

TOXICITY Salmo trutta (brown trout), Lepomis macrochirus (bluegill sunfish), Carassius auratus (goldfish): 2 fish each species; test compound concentration, 5 ppm by weight; exposure 24 hours. No injury. [291]

USE Protectant of materiel.

5. ACRYLONITRILE

ALTERNATIVE NAMES Vinyl cyanide; Propenenitrile; Cyanoethylene.

MOLECULAR FORMULA C_3H_3N

STRUCTURAL FORMULA $CH_2=CHCN$

PHYSICAL AND CHEMICAL PROPERTIES Colorless liquid [118]. Mild odor [53]. Molecular weight, 53.062. Freezing point, $-82^{\circ}C$ [118], $-83.71^{\circ}C$ [70]. Boiling point, $73.97^{\circ}C$ [70], $75-77^{\circ}C$ [228], $78-79^{\circ}C$ [118]. Vapor pressure, 114.3 mm Hg ($25^{\circ}C$) [70]. Specific gravity, 0.80848 [70], 0.797 [118]. Refractive index, 1.39093 [70], 1.393 [118]. Soluble in water [228]. Miscible with acetone, carbon tetrachloride, benzene, ether, n-heptane, alcohol [70].

TOXICITY Man. Inhalation causes nausea, vomiting, diarrhea, weakness, headache, and jaundice. Skin contact causes blistering. [71] Erythema and painful blisters of skin [101]. Flushing of face, increased salivation irritation of eyes and nose; respiration at first rapid and deep, then shallow [250]. Weakness, light-headedness, headache, nausea, sneezing, abdominal pain, vomiting, loss of consciousness, asphyxia, death [192].

Animals. LD in rats, 635 ppm. LD in dogs, 110 ppm. [180]

Animal	Dose	mg/kg	Route	Reference
Guinea pig	LD ₅₀	50	p.o.	120
Mouse	LD ₅₀	15	i.p.	120
Mouse	LD	> 20, < 72	p.o.	47, 120
Rabbit	LD ₅₀	250	c.t.	120
Rabbit	LD ₅₀	25	Skin absorption	47
Rat	LD ₅₀	93(81-106)	p.o.	120

Animal	Dose	mg/L	ppm	Exposure Time	Time of Death
Dog	MLC	0.24	110	Continuous	4 hr
Rat	LC ₅₀	1.1	500	4 hr	
Rat	MLC ₁₀₀	1.38	635	4 hr	8 hr

[120]

USE Protectant of material: textiles (mildew resistance).

CAUTION Fumes are toxic; flammable. [53]

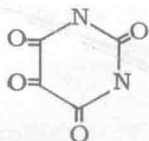
6. ALLOXAN

ALTERNATIVE NAMES Pyrimidinetetrone; Mesoxalylurea.

MOLECULAR FORMULA $C_4H_2N_2O_4$

6. ALLOXAN (Concluded)

STRUCTURAL FORMULA



PHYSICAL AND CHEMICAL PROPERTIES Dark yellow (anhydrous), or colorless (hydrous), rhombic prisms. Molecular weight, 142.072. Decomposes, 170°C. Very soluble in water. Soluble in alcohol. [118]

TESTS In vitro. 10-fold dilutions of test compound added to spores in depression slide cavity; incubated 17 hours.

	$\mu\text{g/sq cm}$	% Inhibition
<u>Stemphylium sarcinaeforme</u> Cav.	1000	100
	100	100
	10	100
	1	64
<u>Sclerotinia fruticola</u> (Wint.) Rehm.	1000	100
	100	52

[55]

Aspergillus niger: 20 ppm inhibited growth 5%; 10 ppm, 5% [228].

TOXICITY

Animal	Dose	mg/kg	Route	Time of Death
Dog	MLD	100	i.v.	Few hr
Dog	LD	75-100	i.v.	1 wk
Mouse	LD ₅₀	300-400	i.p.	48 hr
Mouse	LD ₅₀	200	i.v.	48 hr
Rabbit	MLD	180-250 ¹	r.t. ²	
Rat	LD	300	i.v.	Rapid
Sheep	LD	200	i.v.	24 hr
Duck	MLD	250 ³	i.v.	36-48 hr
Pigeon	LD	150-200	i.v.	2-3 da

[120]

USE Protectant of materiel.

/1/ As alloxan monohydrate, 15% suspension in water. /2/ Or by injection into jejunum.
/3/ 5% solution.

7. ALTERNARIC ACID

SOURCE Alternaria solani (Ell. and Mart.) J. and G.

MOLECULAR FORMULA $C_{21}H_{30}O_8$

PHYSICAL AND CHEMICAL PROPERTIES Thin, colorless, rectangular plates or elongated prisms. Molecular weight, 410.550. Melting point, 138°C. Soluble in ethanol, methanol, pyridine, chloroform, benzene, ether, carbon tetrachloride. Slightly soluble in cold water. Insoluble in petroleum ether. [121] Stable to boiling 5 minutes at pH 3-7.6; partial loss of activity observed after autoclaving at pH 3.0.

TESTS In vitro. Compound active in these tests only at pH 3.5. Minimum concentration required to inhibit spore germination:

	$\mu\text{g/ml}$
<u>Myrothecium verrucaria</u> (Alb. and Schw.) Ditmer ex Fries	0.1
<u>Mucor mucedo</u> Bref.	0.4
<u>Absidia glauca</u> Hagen	0.8
<u>Thamnidium elegans</u> Link	0.8

Minimum concentration required to cause stunting of length of germ tubes and hyphal extension after germination and formation of germ tubes:

	$\mu\text{g/ml}$
<u>Mucor mucedo</u> Bref.	0.001
<u>Thamnidium elegans</u> Link	0.005
<u>Botrytis allii</u> Munn	0.01
<u>Myrothecium verrucaria</u> (Alb. and Schw.) Ditmer ex Fries	0.01
<u>Stemphylium</u> sp	0.04
<u>Absidia glauca</u> Hagen	0.1
<u>Aspergillus tomarii</u> Kita	3.1

[48]

Tests at pH 6.5 proved inactive at comparable concentration levels with the following organisms: Botrytis allii Munn, Fusarium graminearum Schwabe, F. caeruleum (Lib.) Sacc., Penicillium brevicompactum Dierckx, P. digitatum Sacc., Myrothecium verrucaria (Alb. and Schw.) Ditmer ex Fries.

Spore germination of Absidia glauca and Myrothecium verrucaria inhibited at concentrations of 0.1-1.0 $\mu\text{g/ml}$; Botrytis allii at 10.0 $\mu\text{g/ml}$ [121].

PHYTOTOXICITY Toxic to radish, cabbage, carrot and tomato seedlings in concentrations of 1-10 $\mu\text{g/ml}$. May be the chemical agent directly responsible for the disease effects of early blight of potatoes. A crystalline toxin isolated from Alternaria solani filtrates, apparently identical with alternaric acid, produced wilting, epinasty and necrosis in tomato cuttings within a few hours, in dilutions as high as 1:50,000,000. [121]

USE Medicinal.
