WARFARIN
HEALTH AND SAFETY GUIDE

UNITED NATIONS
ENVIRONMENT PROGRAMME

INTERNATIONAL
LABOUR ORGANISATION

WORLD HEALTH
ORGANIZATION

WORLD HEALTH ORGANIZATION, GENEVA 1995
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WARFARIN
HEALTH AND SAFETY GUIDE

This is a companion volume to
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The Environmental Health Criteria (EHC) monographs produced by the International Programme on Chemical Safety include an assessment of the effects on the environment and on human health of exposure to a chemical or combination of chemicals, or physical or biological agents. They also provide guidelines for setting exposure limits.

The purpose of a Health and Safety Guide is to facilitate the application of these guidelines in national chemical safety programmes. The first three sections of a Health and Safety Guide highlight the relevant technical information in the corresponding EHC. Section 4 includes advice on preventive and protective measures and emergency action; health workers should be thoroughly familiar with the medical information to ensure that they can act efficiently in an emergency. Within the Guide is a Summary of Chemical Safety Information which should be readily available, and should be clearly explained, to all who could come into contact with the chemical. The section on regulatory information has been extracted from the legal file of the International Register of Potentially Toxic Chemicals (IRPTC) and from other United Nations sources.

The target readership includes occupational health services, those in ministries, governmental agencies, industry, and trade unions who are involved in the safe use of chemicals and the avoidance of environmental health hazards, and those wanting more information on this topic. An attempt has been made to use only terms that will be familiar to the intended user. However, sections 1 and 2 inevitably contain some technical terms. A bibliography has been included for readers who require further background information.

Revision of the information in this Guide will take place in due course, and the eventual aim is to use standardized terminology. Comments on any difficulties encountered in using the Guide would be very helpful and should be addressed to:

The Director
International Programme on Chemical Safety
World Health Organization
1211 Geneva 27
Switzerland
THE INFORMATION IN THIS GUIDE SHOULD BE CONSIDERED AS A STARTING POINT TO A COMPREHENSIVE HEALTH AND SAFETY PROGRAMME
1. PRODUCT IDENTITY AND USES

1.1 Identity

Common name: warfarin
Chemical formula: C_{19}H_{16}O_{4}

Chemical structure:

![Chemical structure diagram]

Common synonyms: coumafène, warfarine, zoocoumarin

Common trade names: Athrombine-K; Brumolin; Compound 42; Coumadin; Coumafèn; Coumarin; Coumefène; Dethmore; Dethnèl; Eastern States Duocide; Fasco Fascrat Powder; Frass-Ratron; Kumader; Kumadu; Kypfarin; Maag Rattentod Cum; Mar-Frin; Maveran; Panwarfin; Prothromadin; Rat-a-way; Rat-b-gon; Rat-Gard; Rat-Kill; Rat-Mix; Rat-ola; Ratro; Rats-No-More; Rodafarin; Temus W; Warf 42; Warf Compound 42; Warf-12; Warfarat; Warfarin +; Warficide; Zoocoumarin

CAS chemical name: 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one (9CI) (8CI) (I)

IUPAC chemical name: (RS) 4-hydroxy-3-(3-oxo-1-phenylbutyl) coumarin
1.2 Physical and Chemical Properties

Warfarin forms colourless crystals. It is practically insoluble in water, readily soluble in acetone and dioxane and moderately soluble in alcohols. It is acidic. The sodium salts are soluble in water but insoluble in organic solvents.

Further physical and chemical properties of warfarin are given in the “Summary of Chemical Safety Information” (section 6).

1.3 Analytical Methods

The determination of warfarin is mainly based on high-performance liquid chromatography with fluorescence detection. The detection limit in animal tissues is 0.02 mg/kg. The other methods include UV spectrometry and reversed-phase liquid chromatography, the latter with a detection limit in blood serum of 20 µg/litre.

1.4 Production and Uses

The anticoagulant properties of warfarin were reported in 1944, and, in 1948, it was proposed as a rodenticide. Warfarin is used in agriculture and urban rodent control in the form of baits containing 0.025% active ingredient. The sodium salt is available at 0.5% concentrate for use at a final concentration of 0.05% in liquid base. Warfarin is also used as a drug for the treatment of thromboembolic disease in humans.
2. SUMMARY AND EVALUATION

2.1 Identity, Physical and Chemical Properties, and Analytical Methods

Warfarin is a colourless, crystalline compound with a melting point of 151-161 °C. It is practically insoluble in water, readily soluble in acetone and dioxane, and moderately soluble in alcohols. Analytical methods for the determination of warfarin are mainly based on high performance liquid chromatography.

2.2 Sources of Human and Environmental Exposure

Warfarin does not occur naturally. It is used as a rodenticide as well as a drug, and acts by disrupting the normal blood clotting mechanisms causing an increased tendency to bleed.

2.3 Environmental Transport, Distribution, and Transformation

Warfarin is unlikely to enter the atmosphere, because of its low volatility. It is practically insoluble in water. The rate of degradation is relatively slow.

2.4 Environmental Levels and Human Exposure

No information is available on concentrations in air, water, and soil. Warfarin is not intended for direct application to growing crops or for use as a food additive. The controlled medical use of warfarin exposes more people to higher concentrations over a longer period than would be expected to occur as a result of accidental human exposure due to its use as a rodenticide. Accidental overexposures to warfarin as a rodenticide are most commonly reported in children and domestic animals.

2.5 Kinetics and Metabolism in Laboratory Animals and Humans

Warfarin is easily absorbed through the gastrointestinal tract and skin, and is bound to serum proteins. Warfarin is readily hydroxylated in vitro and in vivo by rat liver microsomal enzymes to form 6-, 7-, and 8-hydroxy-warfarin. It is eliminated through both the urine and faeces.
When a single oral dose of 1.5 mg warfarin/kg was given to male and female volunteers, maximum concentration in plasma was reached in 2-12 h. The half-life for disappearance from human plasma ranged from 15 to 58 h.

2.6 Effects on Laboratory Mammals and in vitro Test Systems

The acute oral toxicity of warfarin for rats is high. Reported LD₅₀ values range from 11 to 323 mg/kg, females being more susceptible than males. For classification purposes, the accepted WHO LD₅₀ value is 10 mg/kg. Genetic resistance to warfarin among rodents and humans has been reported. Signs of poisoning are those associated with an increased tendency to bleed.

One study on rats showed some developmental effects. There are no data on mutagenicity.

In feeding studies on rats, the only effect found was associated with anticoagulant action.

2.7 Effects on Humans

Vitamin K functions as an essential element in the synthesis of several blood coagulation factors. Warfarin inhibits this process and consequently affects the blood coagulation mechanisms. Prolonged inhibition of the vitamin K synthesis will lead to severe bleeding and death, if not corrected.

Symptoms of warfarin poisoning begin a few days or weeks after ingestion. They include nose bleeding, bleeding gums, pallor, and, sometimes, haematomas around joints and on the buttocks, and blood in the urine and faeces. Later, paralysis due to cerebral haemorrhage and, finally, haemorrhagic shock and death may occur.

Poisoning incidents have been reported. Outbreaks of poisoning have been observed in relation to warfarin-contaminated meal and also in infants after dermal application of warfarin-contaminated talc. A case of poisoning from prolonged skin contact during the preparation of warfarin baits has also been reported.

Developmental effects known as “warfarin embryopathy” or “fetal warfarin syndrome” were reported when warfarin was administered as a therapeutic agent during pregnancy. No cases of embryopathy following the use of warfarin as a rodenticide have been reported.
2.8 Effects on other Organisms in the Laboratory and Field

Some secondary toxicity laboratory studies on wildlife have shown that captive predators could be intoxicated by sufficient no-choice feeding of warfarin-poisoned rodents.

2.9 Evaluation of Human Health Risks and Effects on the Environment

2.9.1 Evaluation of human health risks

Warfarin is used as both a rodenticide and a drug. In agriculture and urban rodent control, it is used as a tracking dust or bait containing 0.025-0.05% of active ingredient. Increased levels in air, water, and food are unlikely. Occupational exposure may occur during manufacture, formulation, and bait application, but data concerning the levels are not available.

Warfarin is easily absorbed through the gastrointestinal tract and skin, and readily hydroxylated by liver microsomal enzymes in the rat. The half-life for disappearance of warfarin from human plasma has been reported to be between 15 and 58 h.

Warfarin is highly toxic for mammalian species. Signs of poisoning in all species, including humans, are associated with an increased tendency to bleed.

Poisoning incidents after massive oral or dermal exposure have been reported. When used therapeutically, warfarin has been given to patients for long periods without signs of toxicity, other than bleeding. Warfarin is known as a human teratogen. Developmental effects have been observed following the administration of warfarin as a therapeutic agent during pregnancy. No cases of embryopathy following its use as a rodenticide have been reported.

The specific and potent antidote in case of poisoning is vitamin K$_1$.

2.9.2 Evaluation of effects on the environment

Warfarin is applied to discrete sites as low-concentration baits. It is practically insoluble in water and, when it is used as a rodenticide, it is unlikely to be a source of environmental contamination.
Non-target organisms are potentially at risk in two ways: from direct consumption of baits (primary hazard) and through eating poisoned rodents (secondary hazard). The main reason for the poisoning of domestic animals is direct consumption of baits.

Some secondary toxicity laboratory studies have shown that predators can be intoxicated by eating warfarin-poisoned rodents. No cases of secondary poisoning of predators in the field following the use of warfarin as a rodenticide have been found.
3.1 Conclusions

Exposure of the general population to warfarin as a rodenticide through air, drinking-water, or food is unlikely and does not constitute a significant health hazard. Poisoning incidents may occur in cases of massive intentional or unintentional ingestion, massive dermal exposure, and during manufacture and formulation. Warfarin is teratogenic in humans at therapeutic doses. The use of warfarin as a rodenticide is not expected to be a significant source of air, water, soil, or food contamination. Direct or secondary poisoning of birds, domestic and farm animals, and wildlife may occur.

3.2 Recommendations for the Protection of Human Health and the Environment

Potentially exposed workers should receive appropriate biomonitoring and health evaluation.

Exposure of pregnant women to concentrate material must be kept to a minimum. Uneaten baits as well as killed rodents should be burned or buried to reduce the risk of primary or secondary poisonings in non-target organisms.
4. HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

4.1 Human Health Hazards, Prevention and Protection, First Aid

Warfarin is highly toxic for mammalian species, including humans. The probable lethal oral dose in humans is believed to be between 50 and 500 mg/kg. A cumulative total dose of about 1000 mg of warfarin consumed in 13 days has been reported to be fatal for an adult man, equivalent to about 1.1 mg/kg per day.

The main features of warfarin poisoning in less severe cases are excessive bruising, nose and gum bleeding, and blood in the urine and faeces. Bleeding from several organs within the body, leading to shock and possibly death, occurs in the more severe cases. The onset of the signs of poisoning may not be evident until a few days after exposure.

When handling technical material or powder concentrates, full air-fed protection and an impervious suit suitable for wash-down are necessary. Operations with liquid concentrates require the use of PVC or nitrile-rubber gloves, armlets, and an apron, with a face shield and rubber boots.

All persons who are bleeding, or suspected to be heavily exposed, must receive medical attention.

4.1.1 Advice to physicians

If poisoning is recent (within a few hours), gastric lavage is recommended. Administration of active charcoal in repeated doses is also recommended.

Take a venous blood sample for measurement of the haemoglobin level, prothrombin time, blood grouping, and cross-matching.

In less severe cases of poisoning give vitamin K₁ (phytomenadione) (5-10 mg), by slow intravenous infusion, 3 times daily on the first day. After initial intravenous administration, oral treatment can be continued until normalization of prothrombin tests.

In more severe cases, transfusion of matched whole blood or fresh, frozen plasma should also be given and repeated daily until prothrombin tests have returned to normal. Administration of factor concentrate may be considered to prevent a volume overload.
Prothrombin tests should be made at least twice daily until a return to normal is clearly established.

Keep the patient in hospital until the prothrombin time has remained normal for three days.

4.1.2 Health surveillance advice

Workers handling concentrates should undergo periodic determinations of blood prothrombin time. Persons with a history of blood disorders with bleeding tendencies would be expected to be at increased risk in case of exposure.

4.2 Explosion and Fire Hazards

Flash point and flammable limits have not been found. Contact with strong oxidizers may cause fires and explosions. Recommended extinguishers are foam, carbon dioxide, or dry chemicals.

High temperature decomposition or burning may lead to the formation of toxic gases and vapours. Wear full protective clothing and self-contained breathing apparatus in fire-fighting.

Run-off water from the fire should be prevented from entering surface-water drains or water courses.

4.3 Storage

Technical material and formulations should be stored in sealed containers in locked, well-ventilated, dry areas away from frost, direct sunlight, and sources of heat and ignition. Keep products out of reach of children, unauthorized personnel, and domestic animals. Do not store near food or animal feed.

4.4 Transport

Comply with any local regulations regarding the movement of hazardous goods. Before despatch ensure that the containers are sound and that labels are securely fixed and undamaged.
4.5 Spillage

During decontamination, the operator must wear protective clothing, PVC or nitrile gloves, a face shield, and rubber boots.

Small spills should be collected and disposed of as toxic waste according to local legislation.

Large quantities may be destroyed by dissolving in a flammable solvent (e.g., alcohol) and atomizing in a combustion chamber.

Contaminated areas should be washed down with cold water containing surfactant or detergent; the washings must be prevented from entering surface water and drains.

4.6 Disposal

No specific data are available.
Warfarin is practically insoluble in water. It is unlikely to be a source of environmental contamination.

Do not place baits where domestic or farm animals and birds can reach them. Burn or bury any uneaten bait. Do not dump it in water. Look for dead rats and mice and burn or bury them.
6. SUMMARY OF CHEMICAL SAFETY INFORMATION

This summary should be easily available to all health workers concerned with, and users of, warfarin. It should be displayed at, or near, entrances to areas where there is potential exposure to warfarin, and on processing equipment and containers. The summary should be translated into the appropriate language(s). All persons potentially exposed to the chemical should also have the instructions in the summary clearly explained. Space is available for insertion of the National Occupational Exposure Limit, the address and telephone number of the National Poison Control Centre, and local trade names.
SUMMARY OF CHEMICAL SAFETY INFORMATION

WARFARIN

Chemical formula: \( \text{C}_{19}\text{H}_{16}\text{O}_4 \)
CAS chemical name: 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2\(H\)-1-benzopyran-2-one
IUPAC chemical name: (RS) 4-hydroxy-3-(3-oxo-1-phenylbutyl) coumarin
CAS registry number: 81-81-2 (unstated stereochemistry)

<table>
<thead>
<tr>
<th>PHYSICAL PROPERTIES</th>
<th>OTHER CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>crystalline</td>
</tr>
<tr>
<td>Colour</td>
<td>colourless</td>
</tr>
<tr>
<td>Relative molecular mass</td>
<td>308.6</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>159-161</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>insoluble</td>
</tr>
<tr>
<td>Solubility in</td>
<td></td>
</tr>
<tr>
<td>alcohols</td>
<td>moderate</td>
</tr>
<tr>
<td>acetone</td>
<td>readily</td>
</tr>
<tr>
<td>dioxane</td>
<td>readily</td>
</tr>
<tr>
<td>When used as a rodenticide it is formulated as baits containing 250-1000 mg active ingredient/kg</td>
<td></td>
</tr>
</tbody>
</table>

HAZARD SYMPTOMS

GENERAL: Easily absorbed following ingestion and through the skin; if absorbed, may cause increased bleeding tendency to massive haemorrhage

PREVENTION AND PROTECTION

Avoid exposure

FIRST AID

Obtain medical attention; antidote - vitamin K₁
<table>
<thead>
<tr>
<th>SKIN: Absorption may occur</th>
<th>Wear gloves when handling concentrate material</th>
<th>Wash with soap and water; seek medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>EYES:</td>
<td>Use a face shield when handling concentrate material</td>
<td>Flush eyes with water for at least 15 min</td>
</tr>
<tr>
<td>INHALATION: Significant hazard</td>
<td>Avoid breathing aerosols or dust</td>
<td>Move patient to fresh air; call emergency medical care</td>
</tr>
<tr>
<td>INGESTION: An unlikely occupational hazard</td>
<td>Wash hands before eating, drinking, or smoking</td>
<td></td>
</tr>
<tr>
<td>Accidental or intentional ingestion may lead to poisoning in several hours</td>
<td>Keep out of reach of children and under lock and key</td>
<td>Transfer to hospital immediately; rinse out the mouth with water</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPILLAGE</th>
<th>STORAGE</th>
<th>FIRE/EXPLOSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wear protective clothing during decontamination; dry spillage - collect by suction and dispose of as toxic waste; large spillage - dissolve in a flammable solvent for atomizing in a combustion chamber; do not contaminate surface-water drains</td>
<td>Store in sealed containers in a dry, ventilated and locked storeroom, away from children and unauthorized persons, food, and animal feed</td>
<td>Burning in air may lead to the formation of toxic gases and vapours; use alcohol foam, carbon dioxide, or dry chemicals; keep containers cool by spraying with water</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WASTE DISPOSAL</th>
<th>NATIONAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper incineration</td>
<td></td>
</tr>
</tbody>
</table>
7.1 Previous Evaluations by International Bodies

Warfarin has been classified by WHO in Class Ib - Highly Hazardous, based on an acute oral LD₅₀ of 10 mg/kg for rats.

7.2 Exposure Limit Values

- ACGIH TLV, TWA 0.1 mg/m³
- STEL 0.3 mg/m³
- OSHA PEL, TWA 0.1 mg/m³

7.3 Specific Restrictions

Warfarin has been approved for use as a rodenticide in many countries. In some countries, specific uses are defined, as well as limitations and precautions.

7.4 Labelling, Packaging, and Transport

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies warfarin in:

- Packing Group: I — very dangerous substance when active ingredient = 100-60%.
  II—substance presenting medium danger when active ingredient = 60-6%.
  III—substance presenting minor danger when active ingredient 6-1.5% (solid) or 6-0.6% (liquid).

The European Economic Community legislation requires labelling of warfarin as a dangerous substance using the symbol T - toxic.

R 26/27/28 Very toxic by inhalation, in contact with skin, and if swallowed.
7.5 Waste Disposal

In the USA, warfarin waste is identified as an “acute hazardous waste”.


IPCS (1992) Poisons information monograph - Warfarin,


Other HEALTH AND SAFETY GUIDES available:
(continued from inside front cover)

Polybrominated biphenyls (PBBs) (No. 83, 1993)
Polychlorinated biphenyls and polychlorinated
  terphenyls (PCBs and PCTs) (No. 68, 1992)
Propachlor (No. 77, 1992)
Polychlorinated biphenyls and polychlorinated
  Propachlor (No. 77, 1992)
Propylene oxide (No. 15, 1988)
Pyrrolizidine alkaloids (No. 26, 1988)
Quintozene (No. 23, 1988)
Resmethrins (No. 25, 1989)
Rotenone (No. 73, 1992)
TeCNazene (No. 12, 1988)
Tetrachloroethylene (No. 10, 1987)
Tetradifon (No. 11, 1987)
Tetramethrin (No. 31, 1989)
Tri-allate (No. 89, 1994)
Trichlorfon (No. 66, 1991)
Trimellitic anhydride (No. 71, 1992)
Vanadium (No. 42, 1990)
Vinylidene chloride (No. 36, 1989)
Price: Sw. fr. 5.-
Price in developing countries: Sw. fr. 3.50