

# Occupational Health Guideline for Warfarin

## INTRODUCTION

This guideline is intended as a source of information for employees, employers, physicians, industrial hygienists, and other occupational health professionals who may have a need for such information. It does not attempt to present all data; rather, it presents pertinent information and data in summary form.

## SUBSTANCE IDENTIFICATION

- Formula:  $C_{19}H_{16}O_4$
- Synonyms: 3-(alpha-Acetylbenzyl)-4-hydroxycoumarin; WARF compound; compound 42; coumadin
- Appearance and odor: Colorless, odorless solid.

## PERMISSIBLE EXPOSURE LIMIT (PEL)

The current OSHA standard for warfarin is 0.1 milligram of warfarin per cubic meter of air ( $mg/m^3$ ) averaged over an eight-hour work shift.

## HEALTH HAZARD INFORMATION

### • Routes of exposure

Warfarin can affect the body if it is inhaled, if it comes in contact with the eyes or skin, or if it is swallowed. It may enter the body through the skin.

### • Effects of overexposure

Repeated exposure to warfarin may cause bleeding difficulties by impairing the clotting ability of the blood. Problems which may occur include easy bruising, nose bleeds, vomiting blood, bloody or tar-like stools, and bloody urine. A single large dose has been reported to be capable of causing bleeding problems after several days' delay.

### • Reporting signs and symptoms:

A physician should be contacted if anyone develops any signs or symptoms and suspects that they are caused by exposure to warfarin.

### • Recommended medical surveillance

The following medical procedures should be made available to each employee who is exposed to warfarin at potentially hazardous levels:

#### 1. Initial Medical Examination:

—A complete history and physical examination: The purpose is to detect pre-existing conditions that might place the exposed employee at increased risk, and to establish a baseline for future health monitoring. Persons with a history of blood disorders with bleeding tendencies would be expected to be at increased risk from exposure. Examination of the blood should be stressed.

—A complete blood count: Warfarin has been shown to cause hypoprothrombinemia in humans. A complete blood count should be performed including a red cell count, a white cell count, a differential count of a stained smear, as well as hemoglobin and hematocrit.

—Prothrombin time: Warfarin has been shown to cause hypoprothrombinemia in humans. A quick 1-stage prothrombin time or a thrombotest should be performed.

—Urinalysis: Warfarin has been shown to cause an increased bleeding tendency. A urinalysis should be obtained with emphasis on examination for red blood cells as an early indicator of internal bleeding.

2. Periodic Medical Examination: The aforementioned medical examinations should be repeated on an annual basis.

#### • Summary of toxicology

Warfarin as the dust or in solution causes hypoprothrombinemia and vascular injury which results in internal hemorrhage. It suppresses the hepatic formation of prothrombin and of factors VII, IX, and X, causing a markedly reduced prothrombin activity of the blood; it also causes dilation and engorgement of blood vessels and an increase in capillary fragility. The inhibition of prothrombin formation does not become apparent until the prothrombin reserves are depleted, which usually requires exposure for a number of days. A single large

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These recommendations reflect good industrial hygiene and medical surveillance practices and their implementation will assist in achieving an effective occupational health program. However, they may not be sufficient to achieve compliance with all requirements of OSHA regulations.

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exposure may cause intoxication after a latency period of several days, but in a series of acute ingestion episodes there were no signs of hemorrhage or depression of plasma prothrombin. A farmer whose hands were intermittently wetted with a 0.5% solution of warfarin over a period of 24 days developed gross hematuria 2 days after the last contact with the solution; the following day, spontaneous hematomas appeared on the arms and legs. Within 4 days, there was also epistaxis, punctate hemorrhages of the palate and mouth, and bleeding from the lower lip. The bleeding time was over 30 minutes; the clotting time, 11 minutes, 30 seconds; prothrombin index, 17; and the prothrombin percentage (thrombotest), 5. Four days later, after treatment for 2 days with phytonadione, the values were in the normal range. Other effects of warfarin intoxication have included back pain, abdominal pain, vomiting, melena, and petechiae of the skin.

## CHEMICAL AND PHYSICAL PROPERTIES

### • Physical data

1. Molecular weight: 308.3
2. Boiling point (760 mm Hg): Decomposes
3. Specific gravity (water = 1): Greater than 1
4. Vapor density (air = 1 at boiling point of warfarin): Not applicable
5. Melting point: 161 C (322 F)
6. Vapor pressure at 20 C (68 F): Data not available
7. Solubility in water, g/100 g water at 20 C (68 F):

Insoluble

8. Evaporation rate (butyl acetate = 1): Not applicable

### • Reactivity

1. Conditions contributing to instability: None.
2. Incompatibilities: Contact with strong oxidizers may cause fires and explosions.
3. Hazardous decomposition products: Toxic gases and vapors (such as carbon monoxide) may be released in a fire involving warfarin.
4. Special precautions: None.

### • Flammability

1. Flash point: Not applicable
2. Autoignition temperature: Data not available
3. Flammable limits in air, % by volume: Data not available
4. Extinguishant: Foam, carbon dioxide, dry chemical

### • Warning properties

Warfarin is not known to be an eye irritant. It has produced hemorrhages in the retina, however, through its systemic toxicity (Grant).

## MONITORING AND MEASUREMENT PROCEDURES

### • General

Measurements to determine employee exposure are best taken so that the average eight-hour exposure is based

on a single eight-hour sample or on two four-hour samples. Several short-time interval samples (up to 30 minutes) may also be used to determine the average exposure level. Air samples should be taken in the employee's breathing zone (air that would most nearly represent that inhaled by the employee).

### • Method

An analytical method for warfarin is in the *NIOSH Manual of Analytical Methods*, 2nd Ed., Vol. 6, 1980, available from the Government Printing Office, Washington, D.C. 20402 (GPO No. 017-033-00369-6).

## RESPIRATORS

• Good industrial hygiene practices recommend that engineering controls be used to reduce environmental concentrations to the permissible exposure level. However, there are some exceptions where respirators may be used to control exposure. Respirators may be used when engineering and work practice controls are not technically feasible, when such controls are in the process of being installed, or when they fail and need to be supplemented. Respirators may also be used for operations which require entry into tanks or closed vessels, and in emergency situations. If the use of respirators is necessary, the only respirators permitted are those that have been approved by the Mine Safety and Health Administration (formerly Mining Enforcement and Safety Administration) or by the National Institute for Occupational Safety and Health.

• In addition to respirator selection, a complete respiratory protection program should be instituted which includes regular training, maintenance, inspection, cleaning, and evaluation.

## PERSONAL PROTECTIVE EQUIPMENT

• Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent repeated or prolonged skin contact with warfarin or liquids containing warfarin.

• If employees' clothing has had any possibility of being contaminated with warfarin or liquids containing warfarin, employees should change into uncontaminated clothing before leaving the work premises.

• Clothing contaminated with warfarin should be placed in closed containers for storage until it can be discarded or until provision is made for the removal of warfarin from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the warfarin, the person performing the operation should be informed of warfarin's hazardous properties.

• Non-impervious clothing which becomes contaminated with warfarin should be removed promptly and not reworn until the warfarin is removed from the clothing.

## SANITATION

- Skin that becomes contaminated with warfarin should be promptly washed or showered with soap or mild detergent and water to remove any warfarin.
- Eating and smoking should not be permitted in areas where warfarin or liquids containing warfarin are handled, processed, or stored.
- Employees who handle warfarin or liquids containing warfarin should wash their hands thoroughly with soap or mild detergent and water before eating, smoking, or using toilet facilities.

## COMMON OPERATIONS AND CONTROLS

The following list includes some common operations in which exposure to warfarin may occur and control methods which may be effective in each case:

Operation	Controls
Application as a rodenticide	General dilution ventilation; personal protective equipment
Formulation of rodenticides	Local exhaust ventilation; general dilution ventilation; personal protective equipment
Manufacture of warfarin	Personal protective equipment

## EMERGENCY FIRST AID PROCEDURES

In the event of an emergency, institute first aid procedures and send for first aid or medical assistance.

### • Eye Exposure

If warfarin dust gets into the eyes, wash eyes immediately with large amounts of water, lifting the lower and upper lids occasionally. If irritation is present after washing, get medical attention. Contact lenses should not be worn when working with this chemical.

### • Skin Exposure

If warfarin or liquids containing warfarin get on the skin, promptly wash the contaminated skin using soap or mild detergent and water. If warfarin or liquids containing warfarin penetrate through the clothing, remove the clothing promptly and wash the skin using soap or mild detergent and water. Get medical attention promptly.

### • Breathing

If a person breathes in large amounts of warfarin, move the exposed person to fresh air at once. If breathing has stopped, perform artificial respiration. Keep the affected person warm and at rest. Get medical attention as soon as possible.

### • Swallowing

When warfarin has been swallowed and the person is conscious, give the person large quantities of water

immediately. After the water has been swallowed, try to get the person to vomit by having him touch the back of his throat with his finger. Do not make an unconscious person vomit. Get medical attention immediately.

### • Rescue

Move the affected person from the hazardous exposure. If the exposed person has been overcome, notify someone else and put into effect the established emergency rescue procedures. Do not become a casualty. Understand the facility's emergency rescue procedures and know the locations of rescue equipment before the need arises.

## SPILL AND DISPOSAL PROCEDURES

- Persons not wearing protective equipment and clothing should be restricted from areas of spills until cleanup has been completed.

- If warfarin is spilled, the following steps should be taken:

1. Ventilate area of spill.
2. For small quantities, sweep onto paper or other suitable material, place in an appropriate container and burn in a safe place (such as a fume hood). Large quantities may be reclaimed; however, if this is not practical, dissolve in a flammable solvent (such as alcohol) and atomize in a suitable combustion chamber.

- Waste disposal methods:

Warfarin may be disposed of:

1. By making packages of warfarin in paper or other flammable material and burning in a suitable combustion chamber.
2. By dissolving warfarin in a flammable solvent (such as alcohol) and atomizing in a suitable combustion chamber.

## REFERENCES

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## RESPIRATORY PROTECTION FOR WARFARIN

Condition	Minimum Respiratory Protection* Required Above 0.1 mg/m <sup>3</sup>
Particulate Concentration	
0.5 mg/m <sup>3</sup> or less	Any dust respirator, except single-use.
1 mg/m <sup>3</sup> or less	Any dust respirator, except single-use or quarter-mask respirator. Any fume respirator or high efficiency particulate filter respirator. Any supplied-air respirator. Any self-contained breathing apparatus.
5 mg/m <sup>3</sup> or less	A high efficiency particulate filter respirator with a full facepiece. Any supplied-air respirator with a full facepiece, helmet, or hood. Any self-contained breathing apparatus with a full facepiece.
100 mg/m <sup>3</sup> or less	A powered air-purifying respirator with a high efficiency particulate filter. A Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous-flow mode.
200 mg/m <sup>3</sup> or less	A Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure mode or with a full facepiece, helmet, or hood operated in continuous-flow mode.
Greater than 200 mg/m <sup>3</sup> or entry and escape from unknown concentrations	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.  A combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode.
Fire Fighting	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.
Escape	Any dust respirator, except single-use. Any escape self-contained breathing apparatus.

\*Only NIOSH-approved or MSHA-approved equipment should be used.