# Warfarin

| CAS number: | 81-81-2 |
| --- | --- |
| Synonyms: | 3-(Alpha-acetonylbenzyl)-4-hydroxycoumarin, coumarin, 4hydroxy-3-(1-phenyl-3-oxobutyl), athrombine-K, brumlin, coumadin, coumafene, dethmor, kumatox, rodafarin, solfarin, WARF 42 |
| Chemical formula: | C19H16O4 |
| Structural formula: | — |

 Workplace exposure standard (amended)

| TWA: | **0.01 mg/m3** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
|  Notations: | **Sk.** |
| IDLH: | **100 mg/m3** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques.  |

## Recommendation and basis for workplace exposure standard

A TWA of 0.01 mg/m3 is recommended to protect for delayed blood coagulation and developmental toxicity in exposed workers.

## Discussion and conclusions

Warfarin is used as a therapeutic anticoagulant and rodenticide.

The critical effects of exposure are adverse delays in blood coagulation and embryotoxicity.

No human or animal inhalational data are available. Repeat oral doses of 0.2 mg/day cause a decrease in coagulation factor activity of 20 to 30 per cent, which is not associated with adverse effects in humans (ACGIH, 2018; DFG, 2011; HCOTN, 2004). Repeat dosage of 1 mg/day is associated with a significant delay in coagulation (ACGIH, 2018) and 2.5 mg/day causes developmental toxicity in pregnant women (HCOTN, 2004). A NOAEL for developmental toxicity is not reported in the available source material.

Based on the NOAEL of 0.2 mg/day for changes in blood coagulation response, ACGIH (2018) and DFG (2011) extrapolate an equivalent inhalational TWA of 0.01 and 0.02 mg/m3, respectively. ACGIH (2018) applies a factor of two to account for interindividual variability in liver metabolism of the substance, whereas DFG (2011) notes that the 12.5-fold difference between the LOAEL for developmental toxicity and the effective daily intake at the MAK is relatively small. HCOTN (2004) considers an administrative occupational exposure limit (OEL) of 0.1 mg/m3 too high and uses the LOAEL of 2.5 mg/day for developmental toxicity to derive a health-based OEL (HBROEL) of 0.01 mg/m3. In view of these human exposure data and to account for interindividual variability, the TWA of 0.01 mg/m3 derived by ACGIH (2018) and HCOTN (2004) is recommended and expected to be protective of adverse blood coagulation effects and developmental toxicity.

## Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended due to evidence of dermal absorption and contribution to adverse systemic effects.

# Appendix

### Primary sources with reports

| Source Year set Standard  |
| --- |
| SWA 1991 TWA: 0.1 mg/m3 |
|  |
| ACGIH 2016 TLV-TWA: 0.01 mg/m3 |
| TLV-TWA intended to protect for anticoagulation and teratogenic effects observed at high exposures. Vapour pressure varies over wide range. Presence of vapours should be considered in occupational settings. Skin notation recommended based on evidence for systemic effects following dermal absorption in humans and animals.Summary of information:TLV-TWA based on oral dose NOAEL of 0.2 mg/d for blood coagulation effects in humans. Assuming a respiratory volume of 10 m3 during an 8-h shift, an inhalational equivalent is 0.02 mg/m3. A factor of 2 is applied to account for interindividual variabilities in liver metabolism to derive a TLV-TWA of 0.01 mg/m3. Anticoagulant toxicity is cumulative and only appears after normal physiological clotting factors are exhausted. Consequently, repeated doses are required to elicit blood clotting effects. Humans are less sensitive than rodents.Human data: * Significant delay (0.9 s) in coagulation at 1 mg/d in volunteer oral dose study:
	+ NOAEL of 0.2 mg/d (no further details provided)
* Therapeutic oral doses range from 2–10 mg/d depending on patient response, LOAEL of 2 mg/d for clinically significant coagulation effects
* Individuals with kidney or liver diseases, those consuming vitamin K supplements, aspirin or other anticoagulants more susceptible to toxic effects
* Typical effects of overexposure include haemorrhage of the mucous membranes, haematuria, nose bleeds, ecchymoses, pulmonary haemorrhage, uterine haemorrhage, internal haematoma and focal hepatic haemorrhage:
	+ death from massive gastrointestinal bleeding at high doses. Ingestion of 1–2 mg/kg/d fatal
* Maternal ingestion (amount not specified; clinical regimen presented in DFG, 2012) associated with developmental defects, including mid-face hypoplasia, micrognathia, prominent forehead and underdevelopment or absence of nasal septum in a clinical study (n=47):
	+ dose-response and embryotoxic mechanism uncertain
* Haematuria in farmer dermally exposed to 0.5% solution on hands intermittently for 24 d
* Severe dermatitis, without evidence for sensitisation, associated with dermal exposure
* Enzymatically oxidised in liver to inactive metabolites:
	+ polymorphism of enzymes in pathway account for interindividual variability in toxicity
* Plasma t1/2: 36–40 h and whole-body t1/2: ≈1 wk.

Animal data:* 50% mortality at 0.0077 mg/kg/d in repeat dose study (rats, 90 d); comparison with effects of single dose indicates toxicity is cumulative
* Dermal dose of 0.25 mg/kg approximately as effective in increasing blood clotting time as an oral dose of 2 mg/kg (rabbits), 3 dermal applications of 50 mg/kg approximately as effective as 3 oral doses of 0.6 mg/kg (rats).

Insufficient data to recommend a TLV-STEL or notations for carcinogenicity and sensitisation. |
| DFG 2010 MAK: 0.0016 ppm (0.02 mg/m3) |
| Summary of additional information:No human or animal inhalational data available. MAK based on oral NOAEL of 0.2 mg/d for increased coagulation time in humans. Assuming respiratory volume of 10 m3, inhalational equivalent is 0.02 mg/m3; no further UF applied to derive MAK of 0.02 mg/m3 ≡0.0016 ppm. MAK also expected to be protective of embryotoxicity based on a LOAEL of 2.5 mg/d for developmental disorders in humans. An effective daily intake at the MAK would be 0.2 mg/d, which is below the developmental LOAEL, but DFG notes this difference is small.Skin notation recommended based on cases of poisoning from dermal contact in humans and systemic effects in animals following dermal application. A BEI for vitamin K antagonists is available.Human data:* 10–30% reduction in normal coagulation time and increased risk of bleeding at daily intake of 2.5–15 mg/d reported in female patients (no further details provided)
* 20–30% reduction in coagulation factors regarded as adverse effects under workplace conditions due to increased risk of bleeding
* Haemorrhagic syndrome in children (n=741) accidentally exposed to talcum powder contaminated with 1.7–6.5% of warfarin, 177 died
* Increased coagulation time of 20.9 s (normal range 12–14 s) at 0.14 mg/kg/d (9.8 mg/d; n=5, 26 d, not reported in ACGIH, 2018)
* Increased mean coagulation time (0.9 s) at 0.014 mg/kg/d (1 mg/d), NOAEL of 0.003 mg/kg/d (0.2 mg/d; n=7, 3 wk, also reported in ACGIH); NOAEL used to derive MAK
* Warfarin-induced embryopathies found in 22 children of mothers consuming daily doses of 2.5–15 mg/d ≡0.04–0.21 mg/kg/d in the first trimester (between gestation week 6–9) reported in case study of pregnancies (n=418)
* Cases of skin necrosis following therapeutic oral dosing are reported
* Positive patch test with 0.05% solution in petrolatum in 1/350 subjects. DFG considers study inadequate for sensitisation classification.

Animal data:* 32% and 42% decrease in activity of coagulation factors from single dermal dose of 0.25 mg/kg (rabbits) and 0.7 mg/kg (guinea pigs)
* 47% increased coagulation time at 50 mg/kg and 119% at 100 mg/kg reported in repeat dermal dose study with dose groups 0, 10, 50 and 100 mg/kg (rats, 3 d)
* Decreased coagulation activity from 0.4 mg/kg repeat dermal dose, reversible within 5 d following cessation (rabbits, 2 d, dose frequency not specified)
* No carcinogenicity or genotoxicity data available.

Insufficient data to recommend carcinogenicity or sensitiser notations. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2004 TWA: 0.1 mg/m3 |
| Summary of additional information:Current administrative OEL of 0.1 mg/m3 considered too high, hence non-protective. Health based recommended OEL (HBROEL) derived from LOAEL of 2.5 mg/d for teratogenic effects in humans. An overall assessment factor of 30 is applied to account for the severity of the effects and absence of a NOAEL. Assuming a respiratory volume of 10 m3 during an 8-h shift and 100% absorption, HCOTN proposes a HBROEL of 0.01 mg/m3 which is and expected to be protective of developmental toxicity.A skin notation is recommended based on reports of systemic effects in humans following dermal absorption.Human data:* Increased coagulation time in dermally exposed workers. No quantitative results available.
* Cases of developmental adverse effects associated with maternal clinical dose daily regimen of 2.5–15 mg/d:
	+ HCOTN considers 2.5 mg/d or 0.04 mg/kg/d a LOAEL which is used as a POD for deriving the HBROEL
* Adverse developmental effects in 1.5–5% of infants following maternal exposure during therapy with warfarin to prevent blood clotting during the first trimester (wk 6–9 of gestation; also reported in DFG, 2011). CNS effects in 0.5–2% of infants following maternal exposure during treatment in 2nd trimester. These are reported in 2 case studies (n= 418 and 635).

Animal data:* NOAEL of 1 mg/kg/d for embryotoxicity in repeat oral dose developmental study with exposure groups 0, 1, 3, 6, 12, 25, 50, 100 mg/kg/d and concurrent intramuscular injection of 10 mg/kg vitamin K1 (rats, GD 9–20)
* No information on carcinogenicity or genotoxicity available.
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### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| US EPA |  | 1987 | * RfD principally based on clinical data that shows repeat oral doses for therapeutic use of 2–10 mg/d (0.029–0.14 mg/kg/d) are without serious adverse health effects in humans (also presented in ACGIH, 2018), US EPA considers 2 mg/d as the LOAEL for delayed coagulation time.
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| US NIOSH |  | 1994 | * IDLH based on acute toxicity data in humans.
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### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Insufficient data |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Insufficient data |
| **Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations  |
| --- | --- |
| SWA | — |
| HCIS | — |
| NICNAS | NA |
| EU Annex | — |
| ECHA | — |
| ACGIH | Skin |
| DFG | H(skin) |
| SCOEL | NA |
| HCOTN | Skin |
| IARC | NA |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation  |
| --- |
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|  |  |  |  |
| --- | --- | --- | --- |
| Adverse effects in human case study: | yes | 4.00 |   |
| Dermal LD50 ≤1000 mg/kg: | no |   |   |
| Dermal repeat-dose NOAEL ≤200 mg/kg: | yes | 3.00 |   |
| Dermal LD50/Inhalation LD50 <10: |   |   |   |
| *In vivo* dermal absorption rate >10%: |   |   |   |
| Estimated dermal exposure at WES >10%: |   |   |   |
|   |   | 3 | **a skin notation is warranted** |

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### IDLH

| Is there a suitable IDLH value available? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | 308.33 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa:  | 1 ppm = 12.6 mg/m3; 1 mg/m3 = 0.0793 ppm |
| This chemical is used as a pesticide: |[x]
| This chemical is a biological product: |[ ]
| This chemical is a by-product of a process: |[ ]
| A biological exposure index has been recommended by these agencies: | [ ]  ACGIH [x]  DFG [ ]  SCOEL  |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2011) Warfarin und Natriumwarfarin – MAK value documentation.

European Chemicals Agency (ECHA) (2019) Warfarin – REACH assessment.

Health Council of the Netherlands (HCOTN) (2004) Warfarin. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/112.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – Warfarin.

US Environmental Protection Authority (US EPA) (1987) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Warfarin.