Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Warfarin (ISO); 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one

EC number: 201-377-6

CAS number: 81-81-2 [racemic mixture]

CLH-O-0000003175-78-11/F

Adopted

14 March 2014

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPSAL ON WARFARIN (ISO); 4-HYDROXY-3-(3-OXO-1-PHENYLBUTYL)-2H-CHROMEN-2-ONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: warfarin (ISO); 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one
CAS number: 81-81-2
EC number: 201-377-6
Dossier submitter: Ireland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Germany		MemberState	1
Comment received				
In general the German CA supports the classification and labeling proposal. Some minor comments are as follows: Page 4 chapter 1.2 Current classification proposal: please delete symbol "N", because it is not necessary for classification R52/53 (according DSD) Page 5 chapter 1.2 Current classification proposal: please use the right wording for Environmental hazard classification Aquatic Chronic 2 – H411 instead of Env. Chronic Tox.2 Page7 chapter 2 Justification that action is needed…: The current entry in Annex VI table 3.2 is only R52/53 without symbol "N".				
Dossier Submitter's Response				
RAC's response				
Thank you for your comments				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	2
Comment received				
Firstly we would like to thank the Dossier Submitter for the clear analysis of the hazards related with the use of warfarin. Our comments and remarks with respect to the classification for health hazards are listed below: Toxicokinetics On the basis of presented data we agree with conclusions drawn by the Dossier Submitter regarding: fast and extensive absorption of warfarin after oral administration with liver being the main organ of substance accumulation and urinal excretion being an exclusive route of elimination of the substance and its metabolites. Warfarin metabolites were found to have either no or decreased anticoagulant activity in rats liver.				
Dossier Submitter's Response				
Agreed. Thank you for your comment.				

RAC's response
Agreed. Thank you for your comment.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	3
Comment received				
No classification included for this hazard class in annex VI, Tables 3.1 and 3.2 CLP Regulation and no classification is currently proposed (agreement on TC&L in 2006/2007).				
Dossier Submitter's Response				
Agreed. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	4
Comment received				
No classification included for this hazard class in annex VI, Tables 3.1 and 3.2 CLP Regulation and no classification is currently proposed (agreement on TC&L in 2006/2007).				
Dossier Submitter's Response				
Agreed. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	Sweden		MemberState	5
Comment received				

(*ECHA note: The comment below has been submitted as a separate attachment)*

The Swedish CA supports the proposed classification of warfarin as a reproductive toxicant in category 1A regarding developmental toxicity. Warfarin is a well-known human teratogen and the syndrome caused by exposure during early pregnancy is usually referred to as to as warfarine embryopathy (nasal hypoplasia, stippled epiphysis and distal digital hypoplasia1). The presumed mechanism for these effects is similar to the pharmacological/toxicological MoA for effects on coagulation proteins i.e. inhibition of post-translational carboxylation but in this case it is the carboxylation of matrix-gla protein (MGP) in embryonic bone and cartilage extracellular matrix that is affected. Exposure during the second and third trimesters is mainly associated with CNS effects that are thought to be secondary to hemorrhages.

1. Pauli, R.M. (1997). Anticoagulants. In: Drug Toxicity in embryonic development II

(Editors R.J. Kavlock and G.P. Daston), Springer-Verlag, Berlin. p 191 – 229. --- *End of attachment* ---
Dossier Submitter's Response
Agreed. Thank you for your comment.
RAC's response
Agreed. Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	6
Comment received				
Warfarin is already classified as Repr. Cat. 1A.				
Dossier Submitter's Response				
Yes that is correct. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	France		MemberState	7
Comment received				
SCL for reproductive toxicity According to Guidance on the application of the CLP criteria (november 2012), it seems difficult to determine an ED10 based on human data. In this dossier, it was proposed for ED10 to use a therapeutic dose of 2.5 mg/d for which some adverse effects (nasal hypoplasia and vertebral stippling) were observed. However, only one case was reported at this dose (Shaul 1975) and no detailled information was available. In this context, it is difficult to assess the relevance of this choice. Moreover, the choice of 2.5 mg/d led to an internal dose of 0.04 mg/kg/d for a human of 60 kg. This dose is the upper limit value of the dose (ED10) which required a factor of 100 in the derivation of SCL according to CLP guidance. In this context, a SCL of 0.0003% (0.03/100) seems over conservative.				
Dossier Submitter's Response				
Disagree that this is overly conservative. Knowing that Warfarin is a proven human teratogen and considered a class 1 or extremely potent developmental toxicant, the approach detailed in section 6.9 of the CLH report is entirely justified. This followed as closely as the available data allowed, the criteria according to the guidance on the setting of concentration for reproductive toxicants with the CLP Regulation. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment. Based on human data, doses of 2.5-5 mg/person/day (equivalent to 0.04-0.08 mg/kg/day) may cause developmental toxicity and could perhaps be regarded as an ED10 level. This human ED10 value would, if using the guidance for setting SCLs based on animal data, belong to the high potency group (<4 mg/kg/day). The guidance states that for an ED10 <4 mg/kg/day, the SCL is 0.03%, and for ED10 below 0.4 mg/kg/day the SCL				

becomes 0.003%. Also if starting from an ED10 value obtained from animal studies (0.125 mg/kg/day; Kubaszky et al 2009), it would qualify warfarin for the high potency group and result in a SCL of 0.003%. Thus, the RAC is concluding on a SCL on 0.003% for the developmental toxicity of warfarin.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	Germany	HENTSCHKE & SAWATZKI KG	Company-Manufacturer	8
Comment received				
(*ECHA note: The attachment "Warfarin - Comments on the Annex VI report „Proposal for Harmonised Classification and Labelling" is being provided as a separate document to this table)*				
Dossier Submitter's Response				
Disagree. While we welcome the comments from those representing HENTSCHKE & SAWATZKI KG and endorsed by the company in the submitted report we cannot agree with their conclusions - that there is no requirement to set an SCL and instead use the GCL of 0.3% for products containing warfarin. In humans, Warfarin crosses the placenta, and concentrations in foetal plasma approach the maternal values. Warfarin exposure during pregnancy causes a recognised pattern of major congenital malformations (Warfarin embryopathy), foetal haemorrhage, and an increased risk of spontaneous abortion and foetal mortality. It is true that there is insufficient data to determine a true ED10 value based on human data. In this dossier, it was proposed that the lowest individual therapeutic dose (2.5 mg/day or 0.04 mg/kg bw assuming a total bw of 60kg) confirmed to result in human developmental abnormalities (nasal hypoplasia and vertebral stippling) be substituted for the ED10. This is a conservative approach and entirely justified in view of the serious negative effects on human health. We do not have the data to determine if the true ED10 is similar in magnitude to this dose or lies below or above it. Incidental data implies that individuals exposed to warfarin in utero during the first trimester of pregnancy caused a pattern of congenital malformations in about 5% of these individuals. The main problem with trying to compare this incidence with an ED10 value (an effective dose that gives a minimum of a 10% response) is that the response in this case with exposure to pregnant individuals (who constitute a subset to the whole population of treated individuals) and the levels of warfarin used are typically accidental and not planned as would be the situation in a drug development animal study specifically geared to investigating developmental toxicity potential. Information is available in the public domain concerning the incidence of foetal abnormalities in gravid patients with mechanical heart valves who require long-term anticoagulant therapy with warfarin. In the group of 33 gestations, with patients taking a warfarin dose ≤5 mg, there were 28 healthy babies and five foetal complications—four spontaneous abortions in the first trimester of pregnancy and one foetal growth retardation. This equates to an incidence of approximately 15% and would suggest according to the arguments put forward by HENTSCHKE & SAWATZKI KG that the ED10 would in fact be significantly less than a dose of 5mg/day/person. Therefore the value of 2.5 mg/day as an ED10 substitute does not seem entirely unreasonable. Reference: J Am Coll Cardiol. 1999;33(6):1637-1641. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. http://content.onlinejacc.org/article.aspx?articleid=1125744.				
RAC's response				
Thank you for your comment. Based on human data, doses of 2.5-5 mg/person/day (equivalent to 0.04-0.08 mg/kg/day)				

may cause developmental toxicity and could perhaps be regarded as an ED10 level. This human ED10 value would, if using the guidance for setting SCLs based on animal data, belong to the high potency group (<4 mg/kg/day). The guidance states that for an ED10 <4 mg/kg/day, the SCL is 0.03%, and for ED10 below 0.4 mg/kg/day the SCL becomes 0.003%. Also if starting from an ED10 value obtained from animal studies (0.125 mg/kg/day; Kubaszky et al 2009), it would qualify warfarin for the high potency group and result in a SCL of 0.003%. Thus, the RAC is concluding on a SCL on 0.003% for the developmental toxicity of warfarin.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	9
Comment received				
We support following classification of warfarin: Acute Tox. Cat. 2 for oral administration: H300: Fatal if swallowed Acute Tox. Cat. 1 for inhalation: H330: Fatal if inhaled Acute Tox. Cat. 1 for dermal administration: H310: Fatal in contact with skin				
Dossier Submitter's Response				
Agreed. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	France		MemberState	10
Comment received				
SCL derivation SCLs for acute and chronic toxicity should be harmonised between others antocoagulant rodenticides. Difenacoum approach to set SCLs could be used.				
Dossier Submitter's Response				
SCLs for acute toxicity is not applicable under CLP. Reference to other antocoagulant rodenticides was not necessary at the time this dossier was compiled because there was no consensus regarding the approach by the other rodenticides. Instead, reference was made to the Guidance to Regulation (EC) No 1272/2008 for setting of specific concentration limits as explained in section 6.6.5, summary and discussion of repeated dose toxicity. Thank you for your comment.				
RAC's response				
Agreed. SCLs derivation for STOT RE for various AVKs has be harmonised based on the Guidance on the Application of the CLP Criteria. SCLs for acute toxicity is not applicable under CLP. In the opinion of RAC the specific concentration limit for STOT RE for Warfarin should be based on the 90 - day oral study on rats with 90-day LD_{50} in rats = 0.077mg/kg/day. SCL for STOT Rep. 1 of 0.5% is proposed based on serious damage (death) seen at 0.077 mg/kg in the 90-day study in rats. Calculation: 0.077 mg/kg bw/day (adverse effect dose) / 10 mg/kg bw/day (GV for cat. 1) * 100% = 0.77% rounded down to 0.5% as required in the Guidance on the Application of the CLP Criteria . STOT Rep. 2 is proposed between 0.05% and 0.5% using the same data and method of calculation				

using guidance value of 100 mg/kg bw/day for Cat.2. This calculation is performed according to the method described in the Guidance on the Application of the CLP Criteria.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	11
Comment received				
Considering presented results and the CLP ECHA Guideline criteria, we support conclusion of non-classification of warfarin as Skin Irritant 2.				
Dossier Submitter's Response				
Agreed. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	12
Comment received				
We agree on the non-classification of warfarin as Eye irritant 2.				
Dossier Submitter's Response				
Agreed. Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	13
Comment received				
No data available				
Dossier Submitter's Response				
N/A				
RAC's response				
Agreed. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	14
Comment received				
Warfarin classification as STOT RE 1 as well as set specific concentration limits for STOT RE (STOT RE 1 for C ≥ 0.2% and STOT RE 2 for 0.02% ≤ C < 0.2%) are supported by us basing on evidence from human cases in which significant toxicity occurred at low exposure concentrations.				

Dossier Submitter's Response
Agreed. Thank you for your comment.
RAC's response
Thank you for your comment. In the opinion of RAC the specific concentration limit for STOT RE for Warfarin should be based on the 90 - day oral study on rats with 90-day LD_{50} in rats = 0.077mg/kg/day. SCL for STOT Rep. 1 of 0.5% is proposed based on serious damage (death) seen at 0.077 mg/kg in the 90-day study in rats. Calculation: 0.077 mg/kg bw/day (adverse effect dose) / 10 mg/kg bw/day (GV for cat. 1) * 100% = 0.77% rounded down to 0.5% as required in the Guidance on the Application of the CLP Criteria . STOT Rep. 2 is proposed between 0.05% and 0.5% using the same data and method of calculation using guidance value of 100 mg/kg bw/day for Cat.2. This calculation is performed according to the method described in the Guidance on the Application of the CLP Criteria. Evidence from human cases on developmental toxicity of Warfarion was used for derivation of SCL for reproductive toxicity.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Germany		MemberState	15
Comment received				
Page 56 chapter 8.5 Conclusion on the environmental classification and labeling: please use the right wording for Environmental hazard classification Aquatic Chronic 2 – H411 instead of Env. Chronic Tox.2 Please add the cited references in chapter 8 Environmental hazard assessment to the references in Annex 1.				
Dossier Submitter's Response				
IE agrees that the correct wording for Environment hazard classification is Aquatic Chronic 2 – 411, and that this should replace Env. Chronic Tox.2. IE is of the opinion that it is not appropriate to add the cited references in chapter 8 to the references in Annex 1 as the Annex 1 references are from a literature survery conducted by BASF for mammalian toxicology section.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	Finland		MemberState	16
Comment received				
Bioaccumulation: Table 5.3.1.2 "Measured bioaccumulation data" does not seem to include any bioaccumulation results (only a NOEC value is presented). This could be clarified.				
Dossier Submitter's Response				
The BCF value from this study was 21.6 L/kg. This value should replace the NOEC value that is currently in Table 5.3.1.2.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	United Kingdom		MemberState	17
Comment received				
Reference to pesticide/biocide data for warfarin provides acute endpoints on daphnia and algae as well as degradation information, e.g. on hydrolysis and photolysis. This information should ideally be included in the report - but it does not affect the proposed classification.				
Dossier Submitter's Response				
Noted.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	France		MemberState	18
Comment received				
☐ Environmental hazards We agree with the conclusions dealing with biodegradation. We have editorial comments concerning bioaccumulation: 1. Relationship between Kow and BCF is also considered as a QSAR. Therefore it would be better to indicate the reference of such QSAR (TGD) as it has been performed for BCFWIN 2. with BCFWIN 3.0 included in EPIWEB 4.0, slightly higher BCF (28 L/kg) is calculated than reported in CLH report (10.45 L/kg). Nonetheless it should be reminded that warfarin is not in neutral form at environmental pH and QSAR should therefore be applied with caution. 3. In section '5.3.1.2 Measured bioaccumulation data' could you please mention the measured BCF value instead of the NOEC? We have also one editorial comments on aquatic toxicity data: Algae toxicity study: according to the biocidal dossier, a NOEC value has been determined; could you please add these values? We have more concern concerning the acute toxicity. Indeed, provided studies for fish were old and high concentrations of solvent were used, dealing to 40% of death in the solvent control of the key study, and several signs of toxicity in the solvent controls of the supportive studies. Moreover the substance is ready biodegradable, its solubility is low and yet, endpoints are based on nominal concentrations. Additionally, in the supportive studies, unidentified white precipitates are observed. Even if similar results are obtained for the three studies, it could be considered that none of this study is reliable and their results should be interpreted with cautions. To justify that no additional fish toxicity study is required, toxicity data of acetone and information on PEC from the biocide dossier are mentioned. However, even if published data indicate that LD50 for acetone are higher than the used concentration in the test, clear toxicity symptoms are reported in the solvent control of each of the three available studies, and it can therefore not be stated that warfarin cause toxicity in these tests. Additionally, PEC information should not be taken into account for classification and it should be kept in mind that warfarin is used for other purposes than biocidal uses. At last, even if no solvent was used, endpoints for acute toxicity on daphnia are also				

expressed as nominal concentration and reliability of this test is also questionable.

It should be reminded that the PNEC value in biocidal dossier has been derived from chronic toxicity studies, which can explain that good quality acute studies have not been asked in the framework of the biocide directive.

To conclude, in our opinion, acute toxicity data on fish and daphnia are not reliable enough to conclude on aquatic acute toxicity.

Nevertheless, chronic data are reliable and we agree with conclusions dealing with aquatic chronic toxicity: Aquatic Chronic 2 H411.

Dossier Submitter's Response

1. Noted

2. Noted

3. The BCF value from this study was 21.6 L/kg. This value should replace the NOEC value that is currently in Table 5.3.1.2.

Hertl J (2001)-NOE_rC=21.3 mg/L should be added to the table.
Dommröse A-M (1989-supportive data)-NOEC=8.5 mg/L should be added to the table.

Concerns regarding acute toxicity noted. Please see summary in Doc IIIA 7.4.1.1.

Agree that acute studies are unreliable due to the physical and chemical properties of warfarin.

Agree about concerns regarding acute toxicity to fish. The RAC will finalise a decision in this respect.

RAC's response

ATTACHMENTS RECEIVED:

1. **Comments on Annex XV dossiers proposing harmonised Classification & Labelling** (Filename: COM_CLH_PC_Warfarin_SE), submitted on 19.04.2013 by Sweden (*ECHA note: This attachment has been copied under the section Toxicity to Reproduction)*

CONFIDENTIAL ATTACHMENT

1. **Warfarin - Comments on the Annex VI report „Proposal for Harmonised Classification and Labelling", issued November 2012, prepared by the Pesticide Registration and Control Division, Department of Agriculture, Fisheries & Food, Ireland. Proposal for the specific concentration limit (SCL) with respect to developmental toxicity (H360D).** (Filname: Warfarin-SCL-comment_final), submitted on 19.04.2013 by HENTSCHKE & SAWATZKI KG (Company-Manufacturer)