Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Chlorophacinone (ISO); 2-[(4-chlorophenyl)(phenyl)acetyl]-1H-indene-1,3(2H)-dione

EC number: 223-003-0

CAS number: 3691-35-8

CLH-O-0000003643-75-02/F

Adopted

14 March 2014

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPSAL ON CHLOROPHACINONE (ISO); 2-[(4-CHLOROPHENYL)(PHENYL)ACETYL]-1H-INDENE-1,3(2H)-DIONE

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.

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Substance name: chlorophacinone (ISO); 2-[(4-chlorophenyl)(phenyl)acetyl]-1H-indene-1,3(2H)-dione
EC number: 223-003-0
CAS number: 3691-35-8
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	Denmark		MemberState	1
Comment received				
Danish comments to the CLP report on chlorophacinone: Denmark agrees with the classifications proposed by the Spanish rapporteur for the end-points of acute and repeated dose toxicity as well as for aquatic toxicity for chlorophacinone. Denmark does not agree with the proposal not to classify chlorophacinone for developmental toxicity. Denmark's position is that chlorophacinone should be classified as repro cat 1; R61/Repro cat 1A; H 360D. It was agreed in 2007 by the TC C&L group to classify all anticoagulant rodenticides of the coumarin-family as R61 (DSD) (corresponding to H360D according to CLP criteria) due to their structural and mechanistical similarity with warfarin, which is a known human teratogen classified as Repr. Cat 1; R61 (DSD), recognising that the OECD 414 guideline has limitations as to showing the teratogenic effects seen in humans. We do not agree that the new rat study on warfarin according to OECD 414 is sufficient to validate the negative findings in the studies with chlorophacinone. In the new study according to OECD 414 on warfarin, which includes two prenatal dosing windows (6-15 and 6-19), an extra high dose group was added some time after the beginning of the study. The time shift makes it difficult to fully include this dose group in the assessment of the study outcome. Also the study, although showing some developmental effects in the rats, does not mirror the embryopathy picture seen in humans. Due to the differences in development of the neonate rat and human, postnatal dosing would be required in order for an effect as one of the human effects of warfarin, nasal hypoplasia, to be detected. Therefore, the concern that the OECD 414 protocol is not adequate to show developmental effects of AvKs remains. In conclusion, the Danish CA therefore still supports that read-across to the known developmental toxicant warfarin should be applied and that chlorophacinone, as all AvKs,				

should be classified as Repr cat 1; R61 (DSD)/Repro cat1A; H360D (CLP).

Denmark supports the proposed specific concentration limits for chlorophacinone for acute and repeated dose toxicity both in relation to directive 67/458/EC and, for repeated dose toxicity, in relation to CLP regulation 1272/2008. The Danish CA also supports the M-factors proposed for acute and for chronic aquatic toxicity are also supported.

Dossier Submitter's Response

ES:

As several comments have common issues, this is a common response for all the comments related with proposal of classification for developmental toxicity.

The situation is as follows:

The teratogenic studies of chlorophacinone under GLP with OCDE 414 protocol in rat and rabbit at doses with maternal toxicity did not showed developmental effects
No human data showing developmental, embryotoxic, foetotoxic effect are available
There are many evidences that chlorophacinone show identical mode of action for showing hemorrageas based in the same anti Vit K mechanism by inhibiting Vit K epoxide-reductase.

Warfarin have showed embryotoxicity in human. The most prevalent effects were related with foetotoxicity (like birth weight of infants, stillbirth, prematurity, miscarriage end of a pregnancy, , spontaneous abortion, reduced gestation age, prematurity, neonatal death). This mainly associated with exposure during first trimester. This is called warfarin embryopathy of warfarin foetal syndrome.

Teratogenic effect with defects at birth are also showed but less frecquently and mainly associated with exposure during 2^{nd}-3^{rd} trimester and not considered the so called warfarin fetal syndrome. Therefore the most dominant effects of warfarin are related with foetotoxicity. This is well known and can be read in text books and other popular sources of information. Moreover an epidemiological multicentre study in 2006 demonstrates this incidence.

A CEFIC study following 414 protocol have showed mainly the foetotoxicity effects described in humans. Bone malformations is not reproduced in this rat study and therefore also coherent with the human epidemiological data that the main prevalent effects are related with foetotoxicity and not teratogenic effects

The Specialized Expert meeting conclusion in 2006 was emitted in a context and based in the assumption that the standard guideline protocol cannot show the hypothesized developmental toxicity of AVKs rodenticides. However the recent study with warfarin has demonstrated that the guideline test can show the most prevalent known effect of warfarin in humans, although bone malformation are not clearly observed and also no nasal hypoplasia is observed but there are studies demonstrating than is caused with postnatal exposure.

It has been demonstrated that warfarin pass the placenta and so exposure is occurring and also with floucomacen. The physicochemical properties of chlorophacinone compared with warfarin and floucomacen suggest that chlophacinone can also pass the placenta. Therefore if chlorophacinone also cross the placenta why it does not cause the same effect that

observed with warfarin? It is evidence that something is different between warfarin and chlorophacinone. Also chlorophacinone are not causing bleedings in the pups like with warfarin. It has been argued that absence of bleedings is not unique to chlorophacinone and cannot explain the absence of nasal hypoplasia. We agree but we consider that the negative observation of absence of bleeding and the absence of nasal hypoplasia with chlorophacinone cannot be the argument for classification.
The no observation of nasal hypoplasia in the study with warfarin because for that postnatal exposure is needed in rats, is not a demonstration that nasal hypoplasia is produced by chlorophacinone.
It has been argued also that as no effect is observed in teratogenic study should be classified by read across from warfarin based on the "weight of evidence". However these are actually arguments on the basis of the "lack of evidence". In our consideration this is not a scientific valid way of argumentation to support classification. It is "believed/assumed" that the substance is causing teratogenic or embryotoxic effect. As we cannot see the effects, it is argued that the methods are not appropriate for seeing them. The fact that the study in rat are not reproducing ALL the effect observed in human, including those less common, cannot be considered a demonstration that they are occurring with chlorophacinone. This kind or arguments are a round vicious circle of arguments based on negative observations.

Therefore ES-MS still consider that classification is not warranted and the conclusion of the SE-meeting in 2006 is not currently valid considering the current available information.

In any case, considering all the suggested arguments, considering the uncertainties, and considering the concern showed by other MSs, ES would accept the possibility of classification as DSD Category 3 / CLP category 2 but that there are not appropriate evidences for classification as Cat 1A or 1B for reproduction-development.

In relation to the SCL for developmental toxicity for Chlorophacinone, the SCL of 0.003% is proposed based in the following assessment:

Assuming that Chlorophacinone may induce developmental effects at dose levels just below lethal dose levels, this results in a starting value of 5µg/Kg bw/day based on the highest dose level without mortality in the oral 90 day study in rats. According to the guidance, a SCL of 0.003% is proposed for Chlorophacinone because the starting value of 0.005mg/Kgbw/day is 100 fold below the limit of 4mg/Kgbw/day. Therefore,, the SCL for Chlorophacinone shold be set to: 0.3%/100=0.003%

RAC's response

Thank you for the comment.
The RAC is also of the opinion that Chlorophacinone should be classified for developmental toxicity. For all evaluated AVK rodenticides, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and classification as Repr. 1B, i.e. "presumed human reproductive toxicant" is proposed: Based on the known developmental toxicity of the AVK rodenticide Warfarin in humans (Repr. Cat 1A), the reproductive toxicity of Chlorophacinone has been analysed in detail. It is acknowledged that the animal developmental toxicity studies on Warfarin are weakly positive and that the animal developmental toxicity studies on Chlorophacinone are negative. However, in comparison with Warfarin, Chlorophacinone and 2nd generation AVKs have higher acute and repeated dose toxicity, steeper dose-response curves, and longer

half-lives in the exposed organisms, making the evaluation of developmental effects of these rodenticides difficult. Thus, relatively low doses in repeated exposure during gestation lead to maternal toxicity and lethality which hinders the detection of developmental toxicity at higher doses.
As there are no data on the outcome of maternal exposure to Chlorophacinone in humans, classification in category 1A is not considered to be applicable for Chlorophacinone.
Based on the assumption that all AVK rodenticides, including Warfarin and other anticoagulant coumarin pharmaceuticals (see below) share the same MoA, namely inhibition of vitamin K epoxide reductase (VKOR), the assessment of Chlorophacinone includes consideration of the total data base for the AVKs. A weight of evidence assessment resulted in the conclusion that Chlorophacinone has the capacity to adversely affect human *in utero* development. Therefore, a classification as Repr. 1B 1B is proposed with the reasoning given below.
The reasons for this conclusion are:

- Chlorophacinone shares the same MoA as expressed by other anticoagulant AVK rodenticides and coumarin –based pharmaceuticals (inhibition of vitamin K epoxide reductase, an enzyme involved with blood coagulation and foetal tissues development, including bone formation, CNS development and angiogenesis)
- Warfarin and 2 other coumarin pharmaceuticals (acenocoumarol, phenprocoumon) have been shown to cause developmental toxicity in humans.
- One of the 2nd generation AVK rodenticides (Brodifacoum) has been shown to cause foetal effects in humans, possibly after one or a few exposures.
- For AVK rodenticides with a long half-life in the body, even single exposures might suffice to trigger developmental effects. However, such studies are normally not conducted and effects of single dose exposure cannot be detected in standard OECD 414 test where instead the repeated exposure may lead to maternal mortality with steep dose-response.
- The standard animal studies do not pick up all developmental toxicity effects of the AVK rodenticides, most notably the face and CNS malformations that are characteristic for Warfarin and other AVK coumarin pharmaceuticals.
- The most sensitive window for face malformations in humans is the first trimester. Thus, even if some AVK rodenticides may have a lower degree of placental transfer than Warfarin, this will not affect the face malformation hazard.

Not all steps of the MoA in the target tissues liver and bone have been proven, thus introducing some uncertainty in the assessment. However, the RAC is of the opinion that the uncertainty is not sufficient to warrant a Repr. 2 classification.

Reliable evidence of an adverse effect on reproduction in humans, which is required for Repro 1A, was not available for Chlorophacinone, but a potential for human developmental toxicity is presumed based on the weight of evidence assessment above, and RAC thus proposes classification as Repr. 1B, i.e. "presumed human reproductive toxicant".

Regarding a specific concentration limit (SCL) for reprotoxicity, it is acknowledged that the specific data on developmental toxicity of Chlorophacinone are too scarce to guide the setting of the SLC.
Sufficient data to set SCL for developmental toxicity is only available for Warfarin: 0.003% based on human data (with doses of 0.04-0.08 mg/kg/day that may cause developmental toxicity in women regarded as an ED10 level) and on animal data (0.125 mg/kg/day from Kubaszky et al., 2009). As the other AVK rodenticides are equally or more toxic than Warfarin, it is not considered appropriate to apply the generic concentration limit for these substances (0.3%), but rather to base the SCLs on the SCL proposed for Warfarin. Thus, the RAC is of the opinion that the SCL for Warfarin can be used as a surrogate SCL for the other AVK rodenticides, resulting in a SCL of 0.003% for all AVK rodenticides, including

Chlorophacinone.

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	France		MemberState	2
Comment received				
FR disagrees with the classification proposal for human health. Chlorophacinone should be classified Repr. Cat1; R61 – Repr. 1A H360D FR is in accordance with the environmental classification proposal : - CLP Regulation: • Aquatic Acute. 1 (M=1); H400 - very toxic to aquatic life; • Aquatic Chronic. 1 (M=1); H410 – very toxic to aquatic life with long lasting effects - Directive 67/548/EEC: • N; R50-53 – very toxic to organisms, may cause long-term adverse effects in the aquatic environment.				
Dossier Submitter's Response				
See response to Comment 1 (Denmark)				
RAC's response				
Thank you for the comment. The RAC is also of the opinion that Chlorophacinone should be classified for developmental toxicity. For all AVK rodenticides evaluated at this time, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and classification as Repr 1B, i.e. "presumed human reproductive toxicant" is proposed (please see the justification under RAC response to Comment number 1). The comments on the environmental classification are noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	France	LIPHATECH SAS	Company-Manufacturer	3
Comment received				
Our comments are about Developmental toxicity (section 4.11 of CLH report). As data owner, we support the CLH proposal for Chlorophacinone not to be classified for developmental toxicity. We provide two statements from an Expert toxicologist to strengthen our position. **Teratogenicity of AVK Rodenticides** **Classification by Read-Across from Warfarin is not Correct** **Summary** The conclusion of the Specialised Experts ("SE Conclusion") that the classification of all anti-Vitamin K (AVK) rodenticides as teratogens should be read-across from warfarin is no longer valid. - The SE Conclusion is inadequate by modern standards, since it lacks a clear comparison of the data against the classification criteria. - New data overturn a key consideration on which the SE Conclusion was based (i.e., doubt on the ability of the OECD 414 study design to detect AVK embryopathy). A new OECD 414 study of warfarin now demonstrates method sensitivity. - The SE Conclusion was not based on the most appropriate endpoint, being concerned with teratogenicity when more recent epidemiological data show foetotoxicity in human pregnancies to be of greater incidence.				

The CEFIC teratogenicity study of warfarin demonstrates developmental and foetotoxicity, and therefore confirms sensitivity of the OECD 414 study design. There is clear evidence of specific foetal sensitivity to haemorrhage; borderline evidence of an increase of small foetuses (10-day group only) in the absence of maternal toxicity, and adequate evidence of malformation. The incidences of foetal haemorrhage at the low dose demonstrates the ability of the OECD 414 study design to detect specific foetal sensitivity to warfarin, and therefore the same ability to detect specific foetal sensitivity to the AVKs.

The basis for read-across for developmental toxicity from warfarin to the non-warfarin AVK rodenticides, is therefore invalid.

Careful comparison of the guideline developmental toxicity data for each of the non-warfarin AVKs against the classification criteria therefore show:

- Criteria for classification as CLP Cat 1A are not met. There is no evidence that any of the non-warfarin AVK rodenticides are associated with adverse pregnancy outcomes in humans.
- Criteria for classification as CLP Cat 1B are not met. There is no “clear evidence”, from valid GLP- and guideline- compliant studies, that any of the non-warfarin AVK rodenticides cause an adverse effect on development in animals. Indeed, with the multiplicity of good and reliable studies (for which validity of the model is demonstrated) there is strong evidence that they do not.
- Criteria for classification as CLP Cat 2 (“some evidence”) are not met. There is no evidence from GLP- and guideline- compliant studies, that any of the non-warfarin AVK rodenticides cause an adverse effect on development in animals. Indeed, with the multiplicity of acceptable and reliable studies (for which validity of the model is demonstrated) there is strong evidence that they do not.
- No classification for developmental toxicity is therefore appropriate.

Introduction:

Exponent International Ltd has been retained by the CEFIC RDDG[1] to:

1. Review the Specialised Experts[2] conclusion of September 2006 which recommends the AVK rodenticides be classified as Category 1 developmental toxicants on the basis of read-across from warfarin;
2. Review additional data provided by the CEFIC RDDG (a teratogenicity study of warfarin following OECD Test Guideline 414);
3. Deliver an opinion on the validity of the proposed read-across (from warfarin as a Category 1 developmental toxicant, to therefore all AVKs as Category 1 developmental toxicants);

1. Review of the Specialised Experts Conclusion

a) The SE Conclusion is no longer adequate for modern purposes since it lacks a clear comparison with modern (DSD or CLP) criteria.

b) In addition, recent data amend some of the assumptions from which the conclusion is derived; in particular:

c) The OECD 414 study of warfarin demonstrates sensitivity of the method; it is therefore appropriate to base classification on the actual results achieved in OECD 414 teratogenicity studies with each of the AVKs.

d) Teratogenicity is not the most appropriate human or animal endpoint. It is unusual for teratology to occur in the complete absence of other toxicity. A more usual picture is that teratology occurs as a particularly notable feature, among a spectrum of other foetotoxic change. This would appear to be the clinical picture among the therapeutic AVKs including warfarin. A multicentre prospective clinical trial (Schaefer et al, 2006[3]) examined 666 pregnancies to mothers receiving anticoagulant treatment (with warfarin, phenprocoumon, acenocoumarol, fluindione, or phenindione); birth defects were rare but the more numerous findings were of foetotoxicity – prematurity, miscarriage, decreased mean gestational age at delivery, decreased mean birth weight of term infants. Embryotoxicity (of which the teratology would be only one factor) is more meaningful for protection of the foetus; and is identified in the CEFIC warfarin study. The epidemiology of therapeutic AVKs shows that among human pregnancies foetotoxicity is of higher incidence than teratogenicity; the OECD 414 study of warfarin predominantly shows foetotoxicity. The warfarin-related incidence of foetotoxicity in human pregnancies (as stillbirth, prematurity, small at term) is mentioned in a number of the CLH reports, without drawing appropriate parallels to the warfarin study.

e) The essential evaluation of animal developmental toxicity studies is to assess whether a chemical is able to produce adverse effects in the foetus of experimental animals and whether the foetus is directly affected and/or is more susceptible than the mother. It is not generally

expected that the same effects occur across species. It is however generally accepted that if a chemical is able to produce adverse effects on embryos of experimental animals, it could be a hazard also for human embryos, independently of the specific features of the effect. In the case of the CEFIC study of warfarin, results show that the test was able to identify warfarin as a substance toxic for the conceptus, inducing embryofetal mortality, haemorrhages, and malformations i.e. cataract. It appears to be a reliable test to identify a risk for human foetuses.

f) A placental transfer study demonstrated that there was foetal exposure to both warfarin and flocoumafen (which may also be the case for the other AVKs). These data identify foetal exposure in this study yet there is still a significant difference in the foetotoxic effects observed with warfarin compared to those observed with the other AVKs. For all of the nonwarfarin AVK rodenticides, the key determinant of classification is the absence of effects specific to the foetus in the respective teratogenicity studies despite clear exposure.

g) It is unclear how maternal toxicity is taken into account in the classification process for the AVKs. From the Regulation, classification should address the foetus as an especially sensitive target for toxicity. All evidence of warfarin teratogenicity and foetotoxicity in humans is at levels of maternal 'toxicity' (i.e., therapeutic anticoagulation). Further, comments from at least one MS appear to use a potential concern of maternal Vitamin K depletion leading to the embryopathy, as a reason to discount arguments of the AVKs reaching the foetus. A mechanism dependant entirely on maternal toxicity is however justification to not classify.

2. Comments on the CEFIC teratogenicity study of warfarin[4]

The study is reviewed in the CLH proposal for warfarin, and for that reason a detailed description is not given here. The following observations are however offered:

The study carefully examines dose levels around the limit of maternal toxicity. This is important, since the dose-response curve for teratogenicity can be steep (Schardein, 2000[5]). This might be particularly so with the AVKs, since the dose-response for maternal toxicity is also particularly steep. The study also examines two different periods of exposure: days 6-15 of pregnancy ("TP1", corresponding to the pre-2001 OECD 414 guideline) and days 6-19 of pregnancy ("TP2", corresponding to the revised 2001 OECD 414 guideline).

The warfarin study provides clear evidence (for classification purposes) of specific foetal sensitivity to haemorrhage (i.e., foetal haemorrhage is a dose-related finding, found at the lowest dose level which was not maternally toxic, thus demonstrating detection of specific foetal sensitivity). Both exposure periods (10- and 14-day) were adequate to demonstrate foetotoxicity. In the opinion of this reviewer, the study also showed: borderline evidence of an increase of small foetuses (10-day treatment group only) in the absence of maternal toxicity; and adequate evidence of malformation (cataract, which has been noted in human foetuses from mothers administered warfarin during pregnancy [Hall *et al*., 1980[6]]). Although this study examines dose levels very closely spaced in the maternally toxic range, the incidence of foetal haemorrhage at the low dose is clear demonstration of the ability of the standard "OECD 414" design to detect specific foetal sensitivity to warfarin and the AVKs.

In summary: the study showed maternotoxic effects primarily due to haemorrhages in different organs and mortality. The No Adverse Effect Level (NOAEL) for maternal toxicity was 0.125 mg/kg bw/day.

At the level of conceptus warfarin treatment induced:

- an increase of foetal mortality with a NOAEL of 0.150 mg/kg bw/day;
- a dose related increase of foetal haemorrhages even at the lowest dose tested of 0.125 mg/kg bw/day;
- central ocular cataract (typical malformation of warfarin embryopathy) even at the lowest dose tested of 0.125 mg/kg bw/day.

Warfarin is seen to be embryotoxic and teratogenic in the rat.

For each of the non-warfarin AVK rodenticides, at least one teratogenicity study in rats examines developmental toxicity within the maternally toxic range; in total, nine studies in rats of seven non-warfarin AVKs appear adequate for classification purposes, and demonstrate absence of any form of developmental toxicity. For each of the non-warfarin AVK rodenticides, further adequate studies in rabbit also demonstrate absence of developmental toxicity.

Additional Observations on Reasoning for Read-across from the CLH Reports

Most CLH proposals (March 2013) consider the results of the new OECD 414 study of warfarin, and available placental transfer data.

For all of the non-warfarin AVK rodenticides (with the possible exception of bromadiolone), the animal data are concluded to show no evidence of teratogenicity. In cases where classification is recommended, proposals therefore remain entirely based on the common position of read-across from warfarin.
Current proposals for reproductive classification from the seven non-warfarin AVK CLH proposals range from CLP 1A (4 substances), 1B (one), 2 (one) and no classification (one).
In the CLH report for brodifacoum, comparison with criteria is not considered (no entry).
For bromadiolone, the CLH report concludes teratogenicity in the rabbit, based on dissimilar findings in 3 foetuses at two dose levels. The evaluation however appears inconsistent within the CLH report (evaluated as "may constitute a possible risk" on p48, or "some effects" on p51, or "inconclusive" then "teratogenic" on p 53) and there is no evaluation of "strength" (the reader cannot determine if the evaluation constitutes "clear" or "some" animal evidence). This review notes that the findings fall within the range of spontaneous incidence and show no syndrome. There is no evident consideration of warfarin effects other than teratogenicity (i.e. foetotoxicity) or consideration of human foetotoxicity.
The CLH recommendation for chlorophacinone accepts the new data as adequate to not classify.
For coumatetralyl, the CLH report offers a comparison with criteria. The comparison states "*However, due to the difficulties in the design of an optimal study protocol for the detection of potentially teratogenic effects following exposure to coumatetralyl, no clear conclusion can be drawn from the standard guideline studies.*" This statement is inconsistent with the CEFIC warfarin study results; no explanation is offered as to how the studies of coumatetralyl might significantly differ from the warfarin study design. There is no discussion as to the relevance of foetoxicity in the warfarin study with respect to the human epidemiology. The CLH report postulates that a study including Vitamin K supplementation might be meaningful, and that post-natal exposure (after Howe & Webster, 1994[7]) might also be necessary; neither of which were features of the warfarin study design. It must be noted that the design of Howe & Webster (1992)[8], examining bone growth post-natally in rats, probably differs fundamentally from the process of embryonic cell death and remodeling that occurs during the period of major organogenesis and that is the target of teratogenicity studies. Further, in the teratogenicity studies with coumatetralyl, to overcome the fact that developing rodent fetus is typically evaluated at a time when ossification of the skeleton is incomplete (at gestation day 20 in the rat), the skeletons are double-stained (Alizarin red S and Alcian blue) for a thorough assessment of skeletal development including both ossified and cartilaginous structures.
The CLH report for difenacoum offers no comparison with criteria. The warfarin study is assessed as not having shown malformation using the typical TP1 dosing regimen. There is no consideration of the relevance of embryotoxicity in the warfarin study or in humans. Teratogenicity studies of difenacoum were considered not suitable for determination of teratogenicity, citing a need for postnatal exposure (after Howe & Webster, 1992).
The CLH report for difethialone offers a comparison with criteria. The comparison states: "*Due to the difficulties in the design of an optimal study protocol for the detection of potentially teratogenic effects following exposure to difethialone, no clear conclusion can be drawn from these studies*". This statement is inconsistent with the warfarin study results; no explanation is offered as to how the studies of difethialone might significantly differ from the warfarin study design. The difethialone rat study is also criticized for absence of maternal toxicity at the highest dose (50 µg/kg bw/day), with mortality having been observed only in a pilot study (at 70 µg/kg bw/day); this review notes the dose spacing to be within the range of the (effective) warfarin study. There is no discussion of the relevance of foetotoxicity as seen in the warfarin study and in humans.
The CLH report for flocoumafen contains a comparison with criteria, and notes that the absence of teratogenicity seen with flocoumafen, and placental transfer data, give reason to base a classification on the (negative) animal data. However, the report also states that the placental barrier is not absolute (transfer is diminished, not prevented) and the rat model is not an exact model for humans; hence there remains a possibility for developmental effects in humans. The comparison does not discuss the significance of foetotoxicity as seen in the warfarin study and in humans.
It would therefore appear that none of the CLH reports address the significance of foetotoxicity, as seen in humans and in the rat study of warfarin; and therefore they all fail to address the most appropriate endpoint.

3. Comparison with Criteria

This review offers a detailed comparison with criteria, under the assumption that all of the nonwarfarin AVKs show a clear absence of developmental toxicity in animal studies (i.e. dismissing the bromadiolone interpretation as discussed earlier).

Classification should be based on evidence, not hypothesis.
In comparison to the criteria for DSD Cat 1/ CLP Cat 1A:
There is no epidemiological evidence that the non-warfarin AVK rodenticides cause developmental toxicity in humans.
There is clear epidemiologic evidence that warfarin causes developmental toxicity in humans; and that other AVK anticoagulants used as therapeutics (which do not include the non-warfarin AVK rodenticides) also cause developmental toxicity in humans. However, the criterion for "sufficient epidemiologic evidence" is not met for the non-warfarin AVK rodenticides.
There is evidence to support that, due to absence of effect in appropriately-sensitive teratogenicity studies, the non-warfarin AVK rodenticides are intrinsically different to warfarin.
Because the criterion for "sufficient epidemiologic evidence" is not met for the non-warfarin AVK rodenticides, classification into DSD Cat 1/ CLP Cat 1A is not appropriate.
With respect to DSD Cat 2/CLP Cat 1B:
There is no evidence that the non-warfarin AVK rodenticides cause developmental toxicity in animals.
There is a concern, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans. However, there is evidence that the non-warfarin AVK rodenticides are intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies in both rats and rabbits.
Both warfarin and flocoumafen are seen to cross the placenta. Only warfarin induces clear anticoagulant and developmental effects in the foetus. In contrast, flocoumafen clearly does not.
Therefore, for all of the non-warfarin AVK rodenticides, the key determinant of classification is the absence of effects specific to the foetus in the respective teratogenicity studies.
In the absence of relevant effect in animal studies, and with the demonstration of method sensitivity to warfarin, read-across of warfarin developmental toxicity to the other rodenticidal AVKs becomes a scientifically unjustified extrapolation.
Negative results in adequate studies of the AVK rodenticides are meaningful, and placement in DSD Category 2/ CLP Category 1B is not appropriate.
With respect to DSD Cat 3/ CLP Cat 2:
There is no evidence that the non-warfarin AVK rodenticides cause developmental toxicity in animals.
There is a concern, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans. However, there is evidence that the non-warfarin AVK rodenticides are intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies in both rats and rabbits.
Both warfarin and flocoumafen are seen to cross the placenta. Only warfarin induces clear anticoagulant and developmental effects in the foetus. In contrast, flocoumafen clearly does not.
Therefore, for all of the non-warfarin AVK rodenticides, the key determinant of classification is the absence of effects specific to the foetus in the respective teratogenicity studies.
In the absence of relevant effects in animal studies, and with the demonstration of method sensitivity to warfarin, read-across of warfarin developmental toxicity to the other rodenticidal AVKs becomes a scientifically unjustified extrapolation.
Negative results in adequate studies of the non-warfarin AVK rodenticides are meaningful.
Concern is reduced in that warfarin as a therapeutic is administered to humans orally; operator exposure to rodenticidal biocidal products is dermal; and the skin presents a considerable and effective barrier to the AVK rodenticides.
Placement in DSD Category 3/ CLP Category 2 is not appropriate.
By comparison of evidence with the criteria, no classification for developmental toxicity is appropriate.
In conclusion, ample evidence is provided that a read-across from warfarin teratogenicity to the nonwarfarin AVK rodenticides is not justified from a scientific point of view, based on the results of valid and good quality data. When compared with the criteria for classification, there is inadequate

[1] The CEFIC RDDG is comprised of the following companies: Activa, Babolna-Bio, BASF, Bayer, Bell Laboratories, Hentschke & Sawatzki KG, Laboratorios Agrochem, Liphatech, PelGar and Syngenta who each have joint ownership of this document
[2] Commission Working Group of Specialised Experts on Reproductive Toxicity. ECBI/121/06. Ispra, 19-20 September 2006
[3] Schaefer C, Hannemann D *et al* (2006) Vitamin K antagonists and pregnancy outcome. A multi-centre prospective study. Thromb.Haemost. 95(6) 949-57.

[4] Kubaszky R (2009) Teratology study of Test Item Warfarin Sodium with Rats. Unpublished report 07/396-105P, LAB Research Ltd. CEFIC RDDG.
[5] Schardein J (2000) Chemically induced birth defects. Third edition revised and expanded. Marcel Dekker: New York. ISBN: 0-8247-0265-4
[6] Hall *et al*. (1980). Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J. Med.* 68: 122-140.
[7] Howe AM & Webster WS (1994): Vitamin K – its essential role in craniofacial development. Australian Dental Journal, **39**(2) 88-92.
[8] Howe AM & Webster WS (1992): The warfarin embryopathy: a rat model showing maxillonasal hypoplasia and other skeletal disturbances, Teratology, **46**(4) 379-90

Chlorophacinone
Comment on the CLH proposal, 5 March 2013
Developmental toxicity:

The data owner supports the CLH proposal for chlorophacinone, that chlorophacinone should ***not be classified*** for developmental toxicity.
Careful comparison of the guideline developmental toxicity data for chlorophacinone against the classification criteria show:
- Criteria for classification for developmental toxicity are not met.
  - There is no evidence of chlorophacinone being causally associated with developmental toxicity in humans.
  - There is no evidence from acceptable GLP- and guideline-compliant studies, that Chlorophacinone causes an adverse effect on development in animals.
  - The rat study design is demonstrated to be sensitive to warfarin.
- No classification for developmental toxicity is therefore appropriate.

Reasoning

1. Relevance of the Specialised Experts Conclusion[1]

The Commission Working Group of Specialised Experts on Reproductive Toxicity Specialised Experts concluded ("SE conclusion") in September 2006 that the AVK rodenticides should be classified as human teratogens on the basis of currently available data.
The data owner supports the CLH proposal that the SE conclusion not be a basis for chlorophacinone classification.
The SE Conclusion lacks a clear comparison of evidence with modern (DSD or CLP) criteria. The conclusion is based on an inappropriate endpoint (malformation, not foetotoxicity). The conclusion relies on an assumption (uncertainty that the teratogenicity of warfarin can be detected in pre-natal developmental toxicity studies including OECD guideline 414) for which however no evidence is provided; and is proven incorrect by a more recent OECD 414 study demonstrating developmental toxicity of warfarin. The SE Conclusion is therefore no longer valid.
More details are offered in Exponent's EWC0008.

2. Relevance of the CEFIC teratogenicity study of warfarin[2]

The study is reviewed in the CLH proposal for warfarin, and for that reason a detailed description is not given here. The following observations are however offered:
The study carefully examines dose levels around the limit of maternal toxicity. This is important, since the dose-response curve for teratogenicity can be steep (Schardein, 2000[3]). This might be particularly so with the AVKs, since the dose-response for maternal toxicity is also particularly steep. The study also examines two different periods of exposure: days 6-15 of pregnancy ("TP1", corresponding to the pre-2001 OECD 414 guideline) and days 6-19 of pregnancy ("TP2", corresponding to the revised 2001 OECD 414 guideline).
The warfarin study provides clear evidence (for classification purposes) of specific foetal sensitivity to haemorrhage (i.e., foetal haemorrhage is a dose-related finding, found at the lowest dose level which was not maternally toxic, thus demonstrating detection of specific foetal sensitivity). Both exposure periods (10- and 14-day) were adequate to demonstrate foetotoxicity.
In the opinion of this reviewer, the study also showed: borderline evidence of an increase in small foetuses (10-day treatment group only) in the absence of maternal toxicity; and adequate evidence of malformation (cataract). Although this study examines dose levels very closely spaced in the maternally toxic range, the incidence of foetal haemorrhage at the low dose is clear demonstration of ability of the standard "OECD 414" design to detect specific foetal sensitivity to warfarin and the AVKs.
For chlorophacinone, at least one teratogenicity study in rats examines developmental toxicity at a clearly maternally toxic dose based on mortality; further adequate studies in rabbit also

demonstrate absence of developmental toxicity. There was no evidence of foetotoxicity, in studies closely comparable in design to the effective study of warfarin.

3. Comparison with Criteria

The CLH recommendation for chlorophacinone accepts the new data as adequate to not classify. Industry supports the recommendation. The CLH report however omits a detailed comparison with criteria, which is therefore offered (based on evidence) as follows:

In comparison to the criteria for DSD Cat 1/ CLP Cat 1A:

There is no epidemiological evidence that chlorophacinone causes developmental toxicity in humans.
There is clear epidemiologic evidence that warfarin causes developmental toxicity in humans; and that other AVK anticoagulants used as therapeutics also cause developmental toxicity in humans.
However, the criterion for "sufficient epidemiologic evidence" is not met for chlorophacinone.
Because the criterion for "sufficient epidemiologic evidence" is not met for chlorophacinone, classification into DSD Cat 1/ GHS Cat 1A is not appropriate.

In comparison to the criteria for DSD Cat 2/CLP Cat 1B:

There is no evidence that chlorophacinone causes developmental toxicity in animal studies.
There is a *concern*, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans.
However, there is *evidence* that chlorophacinone is intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies of chlorophacinone in both rats and rabbits. The method used to test chlorophacinone is appropriate and sufficient to detect developmental toxicity of warfarin.
Negative results in adequate animal studies of chlorophacinone are meaningful, and placement in DSD Category 2/ CLP Category 1B is not appropriate.

In comparison to the criteria for DSD Cat 3/ CLP Cat 2:

There is no evidence that chlorophacinone causes developmental toxicity in animal studies.
There is a *concern*, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans. However, there is *evidence* that chlorophacinone is intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies in both rats and rabbits. The method used to test chlorophacinone is appropriate and sufficient to detect developmental toxicity of warfarin.
Negative results in adequate animal studies of chlorophacinone are meaningful.
Concern is reduced in that warfarin as a therapeutic is administered to humans orally; biocidal exposure to rodenticides is dermal; and the skin presents a considerable and effective barrier to the AVK rodenticides.
Placement in DSD Category 3/ CLP Category 2 is not appropriate. No classification for developmental toxicity is appropriate.

Conclusion

Ample evidence is provided that the basis for a read-across from warfarin teratogenicity to chlorophacinone is not valid.
When compared with the criteria for classification, there is inadequate evidence for any classification of chlorophacinone for developmental toxicity.

[1] ECBI/121/06, 20 September 2006. ECB, Ispra.
[2] Kubaszky R (2009) Teratology study of Test Item Warfarin Sodium with Rats. Unpublished report 07/396-105P, LAB Research Ltd. CEFIC RDDG.
[3] Schardein J (2000) Chemically induced birth defects. Third edition revised and expanded. Marcel Dekker: New York. ISBN: 0-8247-0265-4

Dossier Submitter's Response

See response to Comment 1 (Denmark)

RAC's response

Thank you for the comment. The RAC is of the opinion that for AVK rodenticides, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and proposes classification as Repr. 1B, i.e. "presumed human reproductive toxicant" (please see the justification under RAC response to Comment number 1).

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Germany		MemberState	4
Comment received				
Proposal: Please add the Human Health Hazards in Table 1.2 Harmonised classification and labelling proposal; Resulting harmonised classification (future entry in Annex VI, CLP Regulation) (page 7). Justification: Human Health Hazards are missing				
Dossier Submitter's Response				
This is a editorial issue which will be corrected				
RAC's response				
Thank you for the comment.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	France		MemberState	5
Comment received				
Point 4.11, Table 20, page 50. Point 4.11.2, page 52 In the study on rabbits, the NOAEL for maternal toxicity is 10 µg/kg bw/day. The value of 50 µg/kg bw/day was not tested. 4.11.4.3 Development, page 42 Chlorophacinone is part of the same group of chemicals, as warfarin. Chlorophacinone has also the same mode of action as warfarin, which is a well documented human teratogen classified as a reproductive toxicant (Repr. Cat1; R61 – Repr. 1A H360D). Warfarin has been shown to cause teratogenicity in humans and in experimental animals. Based on analogy consideration to warfarin classification of chlorophacinone for developmental toxicity, is relevant. Furthermore, reproductive toxicity studies have been performed on difenacoum. No adverse effect were observed on the offspring, however Difenacoun belongs to AVK, is classified Repr. Cat1; R61 – Repr. 1A H360D, based on read-across from warfarin. Therefore, Chlorophacinone should be classified Repr. Cat1; R61 – Repr. 1A H360D. SCL for reprotoxicity should be harmonized with warfarin.				
Dossier Submitter's Response				
In relation to the comment point 4.11, the mistake will be corrected. In relation to the comment point 4.11.4.3: See response to Comment 1 (Denmark)				
RAC's response				
Thank you for the comment. The RAC is also of the opinion that Chlorophacinone should be classified for developmental toxicity. For all AVK rodenticides evaluated at this time, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and classification as Repr. 1B, i.e. "presumed human reproductive toxicant" is proposed (please see the justification under RAC response to Comment number 1).				

The RAC also proposes that SCL for Chlorophacinone reprotoxicity, as well as for all other AVK rodenticides, is based on the SCL proposed for Warfarin (please see the justification under RAC response to Comment number 1).

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	United Kingdom	Exponent International on behalf of CEFIC RDDG	Industry or trade association	6

Comment received

4.11 toxicity for reproduction:
Agree the proposal to not classify. Data are conclusive but not sufficient for classification. Please see the attached document (Exponent doc ID 1109091.uk0 EWC0008)

Teratogenicity of AVK Rodenticides
Classification by Read-Across from Warfarin is not Correct
Summary

The conclusion of the Specialised Experts ("SE Conclusion") that the classification of all anti-Vitamin K (AVK) rodenticides as teratogens should be read-across from warfarin is no longer valid.
- The SE Conclusion is inadequate by modern standards, since it lacks a clear comparison of the data against the classification criteria.
- New data overturn a key consideration on which the SE Conclusion was based (i.e., doubt on the ability of the OECD 414 study design to detect AVK embryopathy). A new OECD 414 study of warfarin now demonstrates method sensitivity.
- The SE Conclusion was not based on the most appropriate endpoint, being concerned with teratogenicity when more recent epidemiological data show foetotoxicity in human pregnancies to be of greater incidence.
The CEFIC teratogenicity study of warfarin demonstrates developmental and foetotoxicity, and therefore confirms sensitivity of the OECD 414 study design. There is clear evidence of specific foetal sensitivity to haemorrhage; borderline evidence of an increase of small foetuses (10-day group only) in the absence of maternal toxicity, and adequate evidence of malformation. The incidences of foetal haemorrhage at the low dose demonstrates the ability of the OECD 414 study design to detect specific foetal sensitivity to warfarin, and therefore the same ability to detect specific foetal sensitivity to the AVKs.
The basis for read-across for developmental toxicity from warfarin to the non-warfarin AVK rodenticides, is therefore invalid.
Careful comparison of the guideline developmental toxicity data for each of the non-warfarin AVKs against the classification criteria therefore show:
- Criteria for classification as CLP Cat 1A are not met. There is no evidence that any of the non-warfarin AVK rodenticides are associated with adverse pregnancy outcomes in humans.
- Criteria for classification as CLP Cat 1B are not met. There is no "clear evidence", from valid GLP- and guideline- compliant studies, that any of the non-warfarin AVK rodenticides cause an adverse effect on development in animals. Indeed, with the multiplicity of good and reliable studies (for which validity of the model is demonstrated) there is strong evidence that they do not.
- Criteria for classification as CLP Cat 2 ("some evidence") are not met. There is no evidence from GLP- and guideline- compliant studies, that any of the non-warfarin AVK rodenticides cause an adverse effect on development in animals. Indeed, with the multiplicity of acceptable and reliable studies (for which validity of the model is demonstrated) there is strong evidence that they do not.
- No classification for developmental toxicity is therefore appropriate.

Introduction:

Exponent International Ltd has been retained by the CEFIC RDDG[1] to:
1. Review the Specialised Experts[2] conclusion of September 2006 which recommends the AVK rodenticides be classified as Category 1 developmental toxicants on the basis of read-across

from warfarin;
2. Review additional data provided by the CEFIC RDDG (a teratogenicity study of warfarin following OECD Test Guideline 414);
3. Deliver an opinion on the validity of the proposed read-across (from warfarin as a Category 1 developmental toxicant, to therefore all AVKs as Category 1 developmental toxicants);

1. Review of the Specialised Experts Conclusion

a) The SE Conclusion is no longer adequate for modern purposes since it lacks a clear comparison with modern (DSD or CLP) criteria.
b) In addition, recent data amend some of the assumptions from which the conclusion is derived; in particular:
c) The OECD 414 study of warfarin demonstrates sensitivity of the method; it is therefore appropriate to base classification on the actual results achieved in OECD 414 teratogenicity studies with each of the AVKs.
d) Teratogenicity is not the most appropriate human or animal endpoint. It is unusual for teratology to occur in the complete absence of other toxicity. A more usual picture is that teratology occurs as a particularly notable feature, among a spectrum of other foetotoxic change. This would appear to be the clinical picture among the therapeutic AVKs including warfarin. A multicentre prospective clinical trial (Schaefer et al, 2006[3]) examined 666 pregnancies to mothers receiving anticoagulant treatment (with warfarin, phenprocoumon, acenocoumarol, fluindione, or phenindione); birth defects were rare but the more numerous findings were of foetotoxicity – prematurity, miscarriage, decreased mean gestational age at delivery, decreased mean birth weight of term infants. Embryotoxicity (of which the teratology would be only one factor) is more meaningful for protection of the foetus; and is identified in the CEFIC warfarin study. The epidemiology of therapeutic AVKs shows that among human pregnancies foetotoxicity is of higher incidence than teratogenicity; the OECD 414 study of warfarin predominantly shows foetotoxicity. The warfarin-related incidence of foetotoxicity in human pregnancies (as stillbirth, prematurity, small at term) is mentioned in a number of the CLH reports, without drawing appropriate parallels to the warfarin study.
e) The essential evaluation of animal developmental toxicity studies is to assess whether a chemical is able to produce adverse effects in the foetus of experimental animals and whether the foetus is directly affected and/or is more susceptible than the mother. It is not generally expected that the same effects occur across species. It is however generally accepted that if a chemical is able to produce adverse effects on embryos of experimental animals, it could be a hazard also for human embryos, independently of the specific features of the effect. In the case of the CEFIC study of warfarin, results show that the test was able to identify warfarin as a substance toxic for the conceptus, inducing embryofetal mortality, haemorrhages, and malformations i.e. cataract. It appears to be a reliable test to identify a risk for human foetuses.
f) A placental transfer study demonstrated that there was foetal exposure to both warfarin and flocoumafen (which may also be the case for the other AVKs). These data identify foetal exposure in this study yet there is still a significant difference in the foetotoxic effects observed with warfarin compared to those observed with the other AVKs. For all of the nonwarfarin AVK rodenticides, the key determinant of classification is the absence of effects specific to the foetus in the respective teratogenicity studies despite clear exposure.
g) It is unclear how maternal toxicity is taken into account in the classification process for the AVKs. From the Regulation, classification should address the foetus as an especially sensitive target for toxicity. All evidence of warfarin teratogenicity and foetotoxicity in humans is at levels of maternal 'toxicity' (i.e., therapeutic anticoagulation). Further, comments from at least one MS appear to use a potential concern of maternal Vitamin K depletion leading to the embryopathy, as a reason to discount arguments of the AVKs reaching the foetus. A mechanism dependant entirely on maternal toxicity is however justification to not classify.

2. Comments on the CEFIC teratogenicity study of warfarin[4]

The study is reviewed in the CLH proposal for warfarin, and for that reason a detailed description is not given here. The following observations are however offered:
The study carefully examines dose levels around the limit of maternal toxicity. This is important, since the dose-response curve for teratogenicity can be steep (Schardein, 2000[5]). This might be particularly so with the AVKs, since the dose-response for maternal toxicity is also particularly steep. The study also examines two different periods of exposure: days 6-15 of pregnancy

("TP1", corresponding to the pre-2001 OECD 414 guideline) and days 6-19 of pregnancy ("TP2", corresponding to the revised 2001 OECD 414 guideline).
The warfarin study provides clear evidence (for classification purposes) of specific foetal sensitivity to haemorrhage (i.e., foetal haemorrhage is a dose-related finding, found at the lowest dose level which was not maternally toxic, thus demonstrating detection of specific foetal sensitivity). Both exposure periods (10- and 14-day) were adequate to demonstrate foetotoxicity.
In the opinion of this reviewer, the study also showed: borderline evidence of an increase of small foetuses (10-day treatment group only) in the absence of maternal toxicity; and adequate evidence of malformation (cataract, which has been noted in human foetuses from mothers administered warfarin during pregnancy [Hall *et al*., 1980[6]). Although this study examines dose levels very closely spaced in the maternally toxic range, the incidence of foetal haemorrhage at the low dose is clear demonstration of the ability of the standard "OECD 414" design to detect specific foetal sensitivity to warfarin and the AVKs.
In summary: the study showed maternotoxic effects primarily due to haemorrhages in different organs and mortality. The No Adverse Effect Level (NOAEL) for maternal toxicity was 0.125 mg/kg bw/day.
At the level of conceptus warfarin treatment induced:
- an increase of foetal mortality with a NOAEL of 0.150 mg/kg bw/day;
- a dose related increase of foetal haemorrhages even at the lowest dose tested of 0.125 mg/kg bw/day;
- central ocular cataract (typical malformation of warfarin embryopathy) even at the lowest dose tested of 0.125 mg/kg bw/day.

Warfarin is seen to be embryotoxic and teratogenic in the rat.
For each of the non-warfarin AVK rodenticides, at least one teratogenicity study in rats examines developmental toxicity within the maternally toxic range; in total, nine studies in rats of seven non-warfarin AVKs appear adequate for classification purposes, and demonstrate absence of any form of developmental toxicity. For each of the non-warfarin AVK rodenticides, further adequate studies in rabbit also demonstrate absence of developmental toxicity.

Additional Observations on Reasoning for Read-across from the CLH Reports

Most CLH proposals (March 2013) consider the results of the new OECD 414 study of warfarin, and available placental transfer data.
For all of the non-warfarin AVK rodenticides (with the possible exception of bromadiolone), the animal data are concluded to show no evidence of teratogenicity. In cases where classification is recommended, proposals therefore remain entirely based on the common position of read-across from warfarin.
Current proposals for reproductive classification from the seven non-warfarin AVK CLH proposals range from CLP 1A (4 substances), 1B (one), 2 (one) and no classification (one).
In the CLH report for brodifacoum, comparison with criteria is not considered (no entry).
For bromadiolone, the CLH report concludes teratogenicity in the rabbit, based on dissimilar findings in 3 foetuses at two dose levels. The evaluation however appears inconsistent within the CLH report (evaluated as "may constitute a possible risk" on p48, or "some effects" on p51, or "inconclusive" then "teratogenic" on p 53) and there is no evaluation of "strength" (the reader cannot determine if the evaluation constitutes "clear" or "some" animal evidence). This review notes that the findings fall within the range of spontaneous incidence and show no syndrome. There is no evident consideration of warfarin effects other than teratogenicity (i.e. foetotoxicity) or consideration of human foetotoxicity.
The CLH recommendation for chlorophacinone accepts the new data as adequate to not classify.
For coumatetralyl, the CLH report offers a comparison with criteria. The comparison states "*However, due to the difficulties in the design of an optimal study protocol for the detection of potentially teratogenic effects following exposure to coumatetralyl, no clear conclusion can be drawn from the standard guideline studies.*" This statement is inconsistent with the CEFIC warfarin study results; no explanation is offered as to how the studies of coumatetralyl might significantly differ from the warfarin study design. There is no discussion as to the relevance of foetoxicity in the warfarin study with respect to the human epidemiology. The CLH report postulates that a study including Vitamin K supplementation might be meaningful, and that post-natal exposure (after Howe & Webster, 1994[7]) might also be necessary; neither of which were features of the warfarin study design.
It must be noted that the design of Howe & Webster (1992)[8], examining bone growth post-natally in rats, probably differs fundamentally from the process of embryonic cell death and remodeling that occurs during the period of major organogenesis and that is the target of teratogenicity studies.

Further, in the teratogenicity studies with coumatetralyl, to overcome the fact that developing rodent fetus is typically evaluated at a time when ossification of the skeleton is incomplete (at gestation day 20 in the rat), the skeletons are double-stained (Alizarin red S and Alcian blue) for a thorough assessment of skeletal development including both ossified and cartilaginous structures.
The CLH report for difenacoum offers no comparison with criteria. The warfarin study is assessed as not having shown malformation using the typical TP1 dosing regimen. There is no consideration of the relevance of embryotoxicity in the warfarin study or in humans. Teratogenicity studies of difenacoum were considered not suitable for determination of teratogenicity, citing a need for postnatal exposure (after Howe & Webster, 1992).
The CLH report for difethialone offers a comparison with criteria. The comparison states: "*Due to the difficulties in the design of an optimal study protocol for the detection of potentially teratogenic effects following exposure to difethialone, no clear conclusion can be drawn from these studies*". This statement is inconsistent with the warfarin study results; no explanation is offered as to how the studies of difethialone might significantly differ from the warfarin study design. The difethialone rat study is also criticized for absence of maternal toxicity at the highest dose (50 µg/kg bw/day), with mortality having been observed only in a pilot study (at 70 µg/kg bw/day); this review notes the dose spacing to be within the range of the (effective) warfarin study. There is no discussion of the relevance of foetotoxicity as seen in the warfarin study and in humans.
The CLH report for flocoumafen contains a comparison with criteria, and notes that the absence of teratogenicity seen with flocoumafen, and placental transfer data, give reason to base a classification on the (negative) animal data. However, the report also states that the placental barrier is not absolute (transfer is diminished, not prevented) and the rat model is not an exact model for humans; hence there remains a possibility for developmental effects in humans. The comparison does not discuss the significance of foetotoxicity as seen in the warfarin study and in humans.
It would therefore appear that none of the CLH reports address the significance of foetotoxicity, as seen in humans and in the rat study of warfarin; and therefore they all fail to address the most appropriate endpoint.

3. Comparison with Criteria

This review offers a detailed comparison with criteria, under the assumption that all of the nonwarfarin AVKs show a clear absence of developmental toxicity in animal studies (i.e. dismissing the bromadiolone interpretation as discussed earlier).
Classification should be based on evidence, not hypothesis.
In comparison to the criteria for DSD Cat 1/ CLP Cat 1A:
There is no epidemiological evidence that the non-warfarin AVK rodenticides cause developmental toxicity in humans.
There is clear epidemiologic evidence that warfarin causes developmental toxicity in humans; and that other AVK anticoagulants used as therapeutics (which do not include the non-warfarin AVK rodenticides) also cause developmental toxicity in humans. However, the criterion for "sufficient epidemiologic evidence" is not met for the non-warfarin AVK rodenticides.
There is evidence to support that, due to absence of effect in appropriately-sensitive teratogenicity studies, the non-warfarin AVK rodenticides are intrinsically different to warfarin.
Because the criterion for "sufficient epidemiologic evidence" is not met for the non-warfarin AVK rodenticides, classification into DSD Cat 1/ CLP Cat 1A is not appropriate.
With respect to DSD Cat 2/CLP Cat 1B:
There is no evidence that the non-warfarin AVK rodenticides cause developmental toxicity in animals.
There is a concern, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans. However, there is evidence that the non-warfarin AVK rodenticides are intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies in both rats and rabbits.
Both warfarin and flocoumafen are seen to cross the placenta. Only warfarin induces clear anticoagulant and developmental effects in the foetus. In contrast, flocoumafen clearly does not.
Therefore, for all of the non-warfarin AVK rodenticides, the key determinant of classification is the absence of effects specific to the foetus in the respective teratogenicity studies.
In the absence of relevant effect in animal studies, and with the demonstration of method sensitivity to warfarin, read-across of warfarin developmental toxicity to the other rodenticidal AVKs becomes a scientifically unjustified extrapolation.
Negative results in adequate studies of the AVK rodenticides are meaningful, and placement in DSD Category 2/ CLP Category 1B is not appropriate.

With respect to DSD Cat 3/ CLP Cat 2:
There is no evidence that the non-warfarin AVK rodenticides cause developmental toxicity in animals.
There is a concern, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans. However, there is evidence that the non-warfarin AVK rodenticides are intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies in both rats and rabbits.
Both warfarin and flocoumafen are seen to cross the placenta. Only warfarin induces clear anticoagulant and developmental effects in the foetus. In contrast, flocoumafen clearly does not.
Therefore, for all of the non-warfarin AVK rodenticides, the key determinant of classification is the absence of effects specific to the foetus in the respective teratogenicity studies.
In the absence of relevant effects in animal studies, and with the demonstration of method sensitivity to warfarin, read-across of warfarin developmental toxicity to the other rodenticidal AVKs becomes a scientifically unjustified extrapolation.
Negative results in adequate studies of the non-warfarin AVK rodenticides are meaningful.
Concern is reduced in that warfarin as a therapeutic is administered to humans orally; operator exposure to rodenticidal biocidal products is dermal; and the skin presents a considerable and effective barrier to the AVK rodenticides.
Placement in DSD Category 3/ CLP Category 2 is not appropriate.
By comparison of evidence with the criteria, no classification for developmental toxicity is appropriate.
In conclusion, ample evidence is provided that a read-across from warfarin teratogenicity to the nonwarfarin AVK rodenticides is not justified from a scientific point of view, based on the results of valid and good quality data. When compared with the criteria for classification, there is inadequate evidence for classification of the non-warfarin AVKs for developmental toxicity.

[1] The CEFIC RDDG is comprised of the following companies: Activa, Babolna-Bio, BASF, Bayer, Bell Laboratories, Hentschke & Sawatzki KG, Laboratorios Agrochem, Liphatech, PelGar and Syngenta who each have joint ownership of this document
[2] Commission Working Group of Specialised Experts on Reproductive Toxicity. ECBI/121/06. Ispra, 19-20 September 2006
[3] Schaefer C, Hannemann D *et al* (2006) Vitamin K antagonists and pregnancy outcome. A multi-centre prospective study. Thromb.Haemost. 95(6) 949-57.
[4] Kubaszky R (2009) Teratology study of Test Item Warfarin Sodium with Rats. Unpublished report 07/396-105P, LAB Research Ltd. CEFIC RDDG.
[5] Schardein J (2000) Chemically induced birth defects. Third edition revised and expanded. Marcel Dekker: New York. ISBN: 0-8247-0265-4
[6] Hall *et al*. (1980). Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J. Med.* 68: 122-140.
[7] Howe AM & Webster WS (1994): Vitamin K – its essential role in craniofacial development. Australian Dental Journal, **39**(2) 88-92.
[8] Howe AM & Webster WS (1992): The warfarin embryopathy: a rat model showing maxillonasal hypoplasia and other skeletal disturbances, Teratology, **46**(4) 379-90

Dossier Submitter's Response

See response to Comment 1 (Denmark)

RAC's response

Thank you for the comment. The RAC is of the opinion that for AVK rodenticides, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and proposes classification as Repr. 1B, i.e. "presumed human reproductive toxicant" (please see the justification under RAC response to Comment number 1).

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	France	LIPHATECH SAS	Company-Manufacturer	7

Comment received

The section concerned is 4.11 in the CLH report.

The statements provided support the Rapporteur Member State conclusion "Based on the available data, no classification for fertility neither for developmental toxicity for Chlorophacinone seems to be warranted."
Dossier Submitter's Response
RAC's response
Thank you for the comment. The RAC is of the opinion that for AVK rodenticides, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and proposes classification as Repr. 1B, i.e. "presumed human reproductive toxicant" (please see the justification under RAC response to Comment number 1).

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	Sweden		MemberState	8
Comment received				
Comments on Annex XV dossiers proposing harmonised Classification & Labelling The Swedish CA does not support the classification proposal for Chlorophacinone regarding reproductive toxicity. We propose that the classification for Chlorophacinone (as well as for the other AVK rodenticides) should be based on read across to human data for Warfarin (i.e warfarin embryopathy). Therefore, Chlorophacinone should be classified in regards to its developmental toxicity as a reproductive toxicant in category 1A. The AVK rodenticides and warfarin share a common mechanism of action, i.e they inhibit the recycling of vitamin K by inhibiting vitamin K epoxide reductase. As a consequence of this, the post-translational carboxylation of coagulation proteins is affected and an increase in coagulation time is observed. Warfarin is a well-known human teratogen and the syndrome caused by exposure during early pregnancy is usually referred to as warfarine embryopathy (nasal hypoplasia, stippled epiphysis and distal digital hypoplasia[1]). 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 anatomical abnormalities of CNS that are thought to be secondary to hemorrhages. No similar effects on bone formation were observed at fetal examination in studies performed according to OECD TG 414 (new and old version) on warfarin or any other AVK rodenticide. However, as shown by Howe and Webster[2] nasal hypoplasia can indeed be induced in rats, if the pups are dosed postnatally with warfarin. This indicates that the study design of the OECD 414 is not appropriate to detect nasal hypoplasia. Consequently, a possible effect on bone formation process by the six rodenticides has not been properly assessed. The absence of bleedings in the fetuses from OECD TG 414 studies from the AVK rodenticide group (with the exception of warfarin) should thus not be used as an argument to indicate that effect on bone formation process is unlikely. Instead, the absence of reported bleedings in the fetuses treated with the six AVK inhibitors could just as well indicate that it is a very narrow margin between the effect dose for the conceptus and the maternally lethal dose. Interestingly, a case report found in the open literature also				

supports that larger 2nd generation molecules such as brodifacoum (Mw 523) can cross the placenta and cause bleedings and mortalities in dog neonates seemingly without effect on the mother[3]. Some differences in placental transfer and potency are observed in the available data but not to an extent that the relevance of the proposed mechanism behind the warfarine syndrome to humans can be rejected as not being applicable for these AVK rodenticides. In addition, there are no obvious differences in the mammalian toxicity within the AVK rodenticide group to suggest that any of the substances are to be classified differently than the others (see table 1). Chlorophacinone is larger than warfarin when ranked according to molecular weight but is smaller than brodifacoum. Chlorophacinone fits into the overall toxicity pattern of the AVK rodenticides (see table 1). The absence of bleedings in the pups compared to warfarin is not unique to chlorophacinone and cannot explain the absence of nasal hypoplasia in the rats. The difference in placental transfer and lower availability in fetuses of flocoumafen is also not a sufficient reason not to read-across to the human data for warfarin, since it does not suggest that the proposed mechanism behind the warfarin data is irrelevant. In addition it does not suggest that the inherent overall mammalian toxicity of flocoumafen differ from the other AVK rodenticides.

In summary, annex 1, point 1.1.1.3 of the CLP regulation supports a weight of evidence evaluation and the available data shows that the physicochemical properties and the mammalian toxicity profile of all the 2nd generation AVK rodenticides is very similar and this supports read across to the animal data for warfarin and also a read across to the human evidence for teratogenicity of warfarin (table 1). Thus, classification regarding developmental toxicity of all AVK rodenticides (including brodifacoum, chlorophacionone and flocoumafen) as reproductive toxicants in category 1A is warranted.

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.
2. Howe, A.M. and Webster, W.S. (1992): The warfarin embryopathy: a rat model showing maxillonasal hypoplasia and other skeletal disturbances. Teratology. Oct;46(4):379-90.
3. Munday, J.S. and Thompson, L.J. (2003). Brodifacoum toxicosis in two neonatal puppies. Vet. Pathol. 40:216-219

Attachment: Table 1. Physicochemical properties and mammalian toxicity summarized from the hydroxyl coumarin AVK dossiers, substances organized according to molecular weight

RAC's response

Thank you for the comment. The RAC is also of the opinion that Chlorophacinone should be classified for developmental toxicity. For all AVK rodenticides evaluated at this time, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and classification as Repr. 1B, i.e. "presumed human reproductive toxicant" is proposed (please see the justification under RAC response to Comment number 1).

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Germany		MemberState	9

Comment received

Proposal:
Read-across from warfarin with Repr. Cat.1; R61 / Repr. 1A H360D to chlorophacinone and all the 2nd generation rodenticide anticoagulants should be applied.

Justification:

The RMS for chlorophacinon refers to the study of Kubaszky, 2009 (page 71 of the CLH Report) and based on the study results the RMS concludes that the C&L of chlorophacinone with R61 is not warranted (page 7 and 4.11.4 Summary and discussion of reproductive toxicity, page 53 of the CLH Report). DE does not support this proposal since it is not in line with the conclusion of the expert meeting (Specialised Experts, September 2006 Commission Doc ECBI/121/06).

Proposal:
Please also include the following reference, if possible:
Johnson, TL (2009): A placental transfer study of warfarin and flocoumafen in rats. Confidential report of BASF: report no. 2009/7000085, dated 16 July 2009. Study number WIL-234006.

Justification:
The study on placental transfer of warfarin and flocoumafen (for further information on the study see CLH report on flocoumafen) was evaluated by the Netherlands and is included in the CLH report on flocoumafen.
The study demonstrates that flocoumafen, like warfarin, is able to pass the placenta. It is not possible however to quantitatively extrapolate data on foetal exposure between the AVK rodenticides. Therefore, the proposal for chlorophacinone with Repr. Cat.1; R61 / Repr. 1A H360D should be maintained.

Dossier Submitter's Response

See response to Comment 1 (Denmark)

RAC's response

Thank you for the comment. The RAC is also of the opinion that Chlorophacinone should be classified for developmental toxicity. For all AVK rodenticides evaluated at this time, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and classification as Repr. 1B, i.e. "presumed human reproductive toxicant" is proposed (please see the justification under RAC response to Comment number 1).

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	United Kingdom	Exponent International on behald of CEFIC RDDG	Industry or trade association	10

Comment received

4.11 Toxicity for reproduction.
Support that chlorophacinone be not classified for developmental toxicity. Data are conclusive and not sufficient for classification. Please see attached document (Exponent docID 1109091.uk0 EWC0009 - chlorophacinone)

Chlorophacinone
Comment on the CLH proposal, 5 March 2013
Developmental toxicity:
The data owner supports the CLH proposal for chlorophacinone, that chlorophacinone should ***not be classified*** for developmental toxicity.
Careful comparison of the guideline developmental toxicity data for chlorophacinone against the classification criteria show:
- Criteria for classification for developmental toxicity are not met.

- There is no evidence of chlorophacinone being causally associated with developmental toxicity in humans.
- There is no evidence from acceptable GLP- and guideline-compliant studies, that Chlorophacinone causes an adverse effect on development in animals.
- The rat study design is demonstrated to be sensitive to warfarin.

- No classification for developmental toxicity is therefore appropriate.

Reasoning

1. Relevance of the Specialised Experts Conclusion[1]

The Commission Working Group of Specialised Experts on Reproductive Toxicity Specialised Experts concluded ("SE conclusion") in September 2006 that the AVK rodenticides should be classified as human teratogens on the basis of currently available data.
The data owner supports the CLH proposal that the SE conclusion not be a basis for chlorophacinone classification.
The SE Conclusion lacks a clear comparison of evidence with modern (DSD or CLP) criteria.
The conclusion is based on an inappropriate endpoint (malformation, not foetotoxicity). The conclusion relies on an assumption (uncertainty that the teratogenicity of warfarin can be detected in pre-natal developmental toxicity studies including OECD guideline 414) for which however no evidence is provided; and is proven incorrect by a more recent OECD 414 study demonstrating developmental toxicity of warfarin. The SE Conclusion is therefore no longer valid.
More details are offered in Exponent's EWC0008.

2. Relevance of the CEFIC teratogenicity study of warfarin[2]

The study is reviewed in the CLH proposal for warfarin, and for that reason a detailed description is not given here. The following observations are however offered:
The study carefully examines dose levels around the limit of maternal toxicity. This is important, since the dose-response curve for teratogenicity can be steep (Schardein, 2000[3]). This might be particularly so with the AVKs, since the dose-response for maternal toxicity is also particularly steep. The study also examines two different periods of exposure: days 6-15 of pregnancy ("TP1", corresponding to the pre-2001 OECD 414 guideline) and days 6-19 of pregnancy ("TP2", corresponding to the revised 2001 OECD 414 guideline).
The warfarin study provides clear evidence (for classification purposes) of specific foetal sensitivity to haemorrhage (i.e., foetal haemorrhage is a dose-related finding, found at the lowest dose level which was not maternally toxic, thus demonstrating detection of specific foetal sensitivity). Both exposure periods (10- and 14-day) were adequate to demonstrate foetotoxicity.
In the opinion of this reviewer, the study also showed: borderline evidence of an increase in small foetuses (10-day treatment group only) in the absence of maternal toxicity; and adequate evidence of malformation (cataract). Although this study examines dose levels very closely spaced in the maternally toxic range, the incidence of foetal haemorrhage at the low dose is clear demonstration of ability of the standard "OECD 414" design to detect specific foetal sensitivity to warfarin and the AVKs.
For chlorophacinone, at least one teratogenicity study in rats examines developmental toxicity at a clearly maternally toxic dose based on mortality; further adequate studies in rabbit also demonstrate absence of developmental toxicity. There was no evidence of foetotoxicity, in studies closely comparable in design to the effective study of warfarin.

3. Comparison with Criteria

The CLH recommendation for chlorophacinone accepts the new data as adequate to not classify. Industry supports the recommendation. The CLH report however omits a detailed comparison with criteria, which is therefore offered (based on evidence) as follows:

In comparison to the criteria for DSD Cat 1/ CLP Cat 1A:

There is no epidemiological evidence that chlorophacinone causes developmental toxicity in humans.
There is clear epidemiologic evidence that warfarin causes developmental toxicity in humans; and that other AVK anticoagulants used as therapeutics also cause developmental toxicity in humans.
However, the criterion for "sufficient epidemiologic evidence" is not met for chlorophacinone.
Because the criterion for "sufficient epidemiologic evidence" is not met for chlorophacinone, classification into DSD Cat 1/ GHS Cat 1A is not appropriate.

In comparison to the criteria for DSD Cat 2/CLP Cat 1B:

There is no evidence that chlorophacinone causes developmental toxicity in animal studies.
There is a *concern*, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans.

However, there is *evidence* that chlorophacinone is intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies of chlorophacinone in both rats and rabbits. The method used to test chlorophacinone is appropriate and sufficient to detect developmental toxicity of warfarin.
Negative results in adequate animal studies of chlorophacinone are meaningful, and placement in DSD Category 2/ CLP Category 1B is not appropriate.

In comparison to the criteria for DSD Cat 3/ CLP Cat 2:

There is no evidence that chlorophacinone causes developmental toxicity in animal studies.
There is a *concern*, based on warfarin and the therapeutic AVKs that AVKs may cause developmental toxicity in humans. However, there is *evidence* that chlorophacinone is intrinsically different to warfarin, based on absence of foetotoxicity in teratogenicity studies in both rats and rabbits. The method used to test chlorophacinone is appropriate and sufficient to detect developmental toxicity of warfarin.
Negative results in adequate animal studies of chlorophacinone are meaningful.
Concern is reduced in that warfarin as a therapeutic is administered to humans orally; biocidal exposure to rodenticides is dermal; and the skin presents a considerable and effective barrier to the AVK rodenticides.
Placement in DSD Category 3/ CLP Category 2 is not appropriate. No classification for developmental toxicity is appropriate.

Conclusion

Ample evidence is provided that the basis for a read-across from warfarin teratogenicity to chlorophacinone is not valid.
When compared with the criteria for classification, there is inadequate evidence for any classification of chlorophacinone for developmental toxicity.

[1] ECBI/121/06, 20 September 2006. ECB, Ispra.
[2] Kubaszky R (2009) Teratology study of Test Item Warfarin Sodium with Rats. Unpublished report 07/396-105P, LAB Research Ltd. CEFIC RDDG.
[3] Schardein J (2000) Chemically induced birth defects. Third edition revised and expanded. Marcel Dekker: New York. ISBN: 0-8247-0265-4

Dossier Submitter's Response

See response to Comment 1 (Denmark)

RAC's response

Thank you for the comment. The RAC is of the opinion that for AVK rodenticides, including Chlorophacinone, a potential for human developmental toxicity is presumed based on the weight of evidence assessment, and proposes classification as Repr. 1B, i.e. "presumed human reproductive toxicant" (please see the justification under RAC response to Comment number 1).

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	France		MemberState	11

Comment received

Point 1.3, tables 3 and 4, page 9.
The approach for the setting of specific concentration limits (SCLs) for acute and chronic toxicity should be harmonised between anticoagulant rodenticides. Difenacoum approach to set SCLs could be used.

Dossier Submitter's Response

The suggested SCLs for Chlorophacinone have been established according to the Annex I of the Regulation (EC) Nº 1272/2008 (CLP) and following the Guidance on the application of the CLP criteria.

RAC's response

Thank you the comment. SCL for acute toxicity is not applicable under CLP. SCLs derivation for STOT RE for evaluated AVKs has been harmonised.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2013	Finland		MemberState	12
Comment received				
Aquatic toxicity: The proposed classification according to Regulation (EC) No 1272/2008 and 286/2011 for hazardous to the aquatic environment is: Aquatic Acute 1 H400, M-factor 1; Aquatic Chronic 1 H410, M-factor 1. For clarity reason there should also be description how M-factors have been derived in the CLH report.				
Dossier Submitter's Response				
"The proposed M-factor for acute toxicity of 1 is based on the most sensitive specie, Onchorhycnchus mykiss, with a 96hLC50 = 0.45 mg/l; toxicity band between 0.1 mg/l and 1 mg/l) and the proposed SCL: C≥25% N, R50/53 2.5%≤C<25% N, R51/53 0.25%%≤C<2.5% R52/53 Based on the most stringent outcome for Aquatic Chronic toxicity (on the basis of the Algae NOEC and the LC50 for the other trophic levels) an M-factor for chronic toxicity of 1 could be assigned, based on the fish 96LC50=0.45 mg/l and the fact that the substance is not rapidly degradable."				
RAC's response				
Noted and agreed.				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2013	Belgium		MemberState	13
Comment received				
We support the proposed M-factor for acute toxicity of 1(most sensitive species Fish - Onchorhycnchus mykiss with 96hLC50 = 0.45 mg/l; toxicity band between 0.1 mg/l and 1 mg/l) and the proposed SCL : C≥25% N, R50/53 2.5%≤C<25% N, R51/53 0.25%%≤C<2.5% R52/53 Based on the most stringent outcome for Aquatic Chronic toxicity (on the basis of the Algae NOEC and the LC50 for the other trophic levels) an M-factor for chronic toxicity of 1 could be assigned, based on the fish 96LC50=0.45 mg/l and the fact that the substance is not rapidly degradable. Some editorial or/and minor comments Tabel 9(p23) reports a water solubility of 13µg/ml, while the Henry's law constant (p60) is based on a water solubility of 13 mg/l. Please correct.				

Dossier Submitter's Response
We agree
RAC's response
Noted.

ATTACHMENTS RECEIVED:

Teratogenicity of AVK Rodenticides Classification by Read-Across from Warfarin is not Correct (File name: Read-across rebuttal EWC0008), submitted on 19 April 2013 by Exponent International on behalf of CEFIC RDDG (*ECHA's comment: additional information provided in the document copied under Toxicity to reproduction)*

Chlorophacinone, Comment on the CLH proposal, 5 March 2013 (File name: Chlorophacinone classification - developmemtal EWC0009), submitted on 19 April 2013 by Exponent International on behalf of CEFIC RDDG (*ECHA's comment: additional information provided in the document copied under Toxicity to reproduction*)

Teratogenicity of AVK Rodenticides Classification by Read-Across from Warfarin is not Correct (File name: Read-across rebuttal EWC0008), submitted on 19 April 2013 by LIPHATECH SAS (*ECHA's comment: additional information provided in the document copied under General comments*)

Chlorophacinone, Comment on the CLH proposal, 5 March 2013 (File name: Chlorophacinone classification - developmemtal EWC0009), submitted on 19 April 2013 by LIPHATECH SAS (*ECHA's comment: additional information provided in the document copied under General comments*)

Comments on Annex XV dossiers proposing harmonised Classification & Labelling (File name: COM_CLH_PC_Chlorophacinone_SE), submitted on 19 April 2013 by Sweden (*ECHA's comment: additional information copied under Toxicity to Reproduction with the exception of Table 1. Physicochemical properties and mammalian toxicity summarized from the hydroxyl coumarin AVK dossiers, substances organized according to molecular weight)*