Committee for Risk Assessment
RAC

Annex 2
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and labelling at EU level of

TEMBOTRIONE

EC number: N/A
CAS number: 335104-84-2

CLH-O-0000002527-72-03/A2

Adopted
4 June 2013

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

ECHA has compiled the comments received via the internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensively as possible. Please note that some of the comments might occur under several headings, when splitting the information provided is not reasonable.

Substance name: Tembotrione
EC number: -
CAS number: 335104-84-2

Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
25/06/2012	Germany		MSCA	1

Comment received

1.3 Proposed harmonised classification and labelling based on Regulation (EC) No 1272/2008 and/ or DSD criteria

Concerning labelling based on Regulation (EC) No 1272/2008 we like to remark the following:
- The applicable pictograms are GHS07, GHS08 and GHS 09. The missing ones should be added.
- The Hazard statement H400 is part of the classification but not of the labelling and should therefore be omitted here.
- The Precautionary statement "(P102)" should be added in case the substance may be available for the consumer/ general public.
- Having the more stringent Precautionary statement "P260" "P261" should be omitted.
- Finally the Precautionary statement "P321" seems to us not really necessary.

Concerning labelling based on Directive 67/548/EEC we like to remark the following:
- Having "Xn, Harmful" the indication of danger "Xi, Irritant" can be omitted.
- The S-phrase "(S2-)" should be added in case the substance may be available for the consumer/ general public.
- Furthermore the S-phrase "S22" should be added as the substance is a powder.
- On the other hand having the combination "S36/37" the S-phrase "S24" can be deleted.
- And some of the S-phrases (S56, S57) are quite unusual compared to similar labels (R-phrases).
- Finally some S-phrases (S46, S56) are not applicable if the substance is not likely to be used by the consumer/ general public.

Dossier Submitter's Response

Comment noted, the revised proposal is:

Please note that tembotrione is a herbicide and the intended use(s) in Austria are against grasses and broad leaved weeds in corn and sweet corn. No uses in home and garden are intended or authorised. To our knowledge, the situation in other member states is alike. Thus, the substance is not likely to be used by consumers/ the general public.

Labelling based on Directive 67/548/EEC:

Indication of danger:

Xn	Harmful
N	Dangerous for the Environment

R-phrases:

R43	May cause sensitisation by skin contact
R48/22	Harmful: Danger of serious damage to health by prolonged exposure if swallowed
R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S-phrases:

(S2	Keep out of the reach of children)
S22	Do not breathe dust
S36/37	Wear suitable protective clothing and gloves.

Labelling based on Regulation (EC) 1272/2008:

Hazard pictograms: GHS07, GHS08, GHS09

Signal word: Warning

Hazard statements:

H317 (Cat.1B)	May cause an allergic skin reaction
H373 (STOT RE 2)	May cause damage to organs through prolonged or repeated exposure
H400	Very toxic to aquatic life
H410	Very toxic to aquatic life with long lasting effects

Precautionary statements:

(P102	Keep out of reach of children)
P260	Do not breathe dust/fume/gas/mist/vapours/spray
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves/protective clothing/eye protection/face protection.
P314	Get medical advice/attention if you feel unwell.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P363	Wash contaminated clothing before reuse.
P273	Avoid release to the environment.
P391	Collect spillage.
P501	Dispose of contents/container to

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
26/06/2012	France	BCS	Company-Manufacturer / Germany	2

Comment received

On several pages. The CLH document contains many typographical errors which need to be corrected, in particular please change morality to mortality on pages 46 and 84.

On several pages and in particular on page 93 to complete the information provided in the mechanistic studies, please consider the following when evaluating the rat findings.
The main effect of systemic exposure to tembotrione in mammals is inhibition of the enzyme 4-hydroxy-phenylpyruvate dioxygenase (HPPDase), which is involved in the metabolism of the amino acid tyrosine. However, the consequences of HPPDase inhibition are not the same across the species. The rat is the most sensitive one and show specific effects in target organs which are not relevant for human risk assessment as elucidated in a series of mechanistic studies discussed in various section of the CLH.

Dossier Submitter's Response

Comment noted; we apologize for the mistakes

RAC's response

Noted. The RAC has reviewed the literature on tyrosinaemia, and is of the opinion that tyrosinaemia is a relevant mode of action (MoA) in humans. The triketone analogue NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) is used as a pharmaceutical drug to inhibit HPPD, and the potency of tembotrione in humans might not be that much lower than the potency of NTBC. As NTBC has been shown to greatly increase tyrosine concentrations in healthy adult volunteers treated with a single dose of 1 mg/kg/day NTBC (Lock et al, 2001), and to cause eye problems in some children treated with 1 mg/kg/day NTBC against tyrosinaemia type 1, tembotrione can be expected to have an intrinsic possibility to also cause similar problems in humans. Concerning human sensitivity in relation to the animal data, the human sensitivity might be intermediate to that of the very sensitive rat and the non-sensitive mouse. The RAC therefore will consider rat data, but with some reservation for expected lower sensitivity of humans than of rats. Thus, the RAC is of the opinion that human relevance has to be assumed, even though considerable species differences in sensitivity is acknowledged.

Date	Country	Organisation	Type of Organisation	Comment number
27/06/2012	Spain		MSCA	3

Comment received

p.7 Harmonised classification and labelling proposal (Part A; point 1.2)
We agree with the Austrian proposal that tembotrione requires the following classification and labelling:

a) CLP Regulation

H317 "May cause an allergic skin reaction" (Skin Sens. 1), based on the findings in the submitted Maximisation study.

H373 "May cause damage to organs through prolonged or repeated exposure" (STOT RE 2), based on the findings of mortality in pregnant rabbits at the dose level of 100 mg/kg bw/d in a developmental toxicity study.
However, since it has not been conclusively proven that no other routes of exposure (dermal, inhalation) cause the hazard in pregnant rabbits, we consider that the route of exposure should not be stated.

b) Directive 67/548/EEC

R43 May cause sensitisation by skin contact

R48/22 Harmful: Danger of serious damage to health by prolonged exposure if swallowed

Dossier Submitter's Response

Comment has been considered in the response to the general comment number 1

RAC's response

Based on the available data, the sensitisation sub-category 1B is now proposed by the dossier submitter. Strictly based on the data (100% response at 2.5% tembotrione), 1B is appropriate. However, had lower concentrations been tested, it cannot be excluded that >60% of the animals would respond at a concentration of 1%, making it difficult to rule out a higher potency (1A). The RAC is therefore of the opinion that category 1, without defining the sub-category is the correct classification. STOT RE 2 is also supported by RAC, and we also agree that route of exposure should not be stated.

Date	Country	Organisation	Type of Organisation	Comment number
28/06/2012	Denmark		MSCA	4

Comment received

DK agrees with the proposed harmonised classification for Tembotrione. With regard to skin sensitization DK further suggests that the substance should be classified in the relevant subcategory – Cat 1B - for skin sensitization according to the 2.nd ATP to CLP.

Dossier Submitter's Response

Comment has been considered in the response to the general comment number 1

RAC's response

See RAC response to comment number 3.

Date	Country	Organisation	Type of Organisation	Comment number
29/06/2012	Sweden		MSCA	5

Comment received

We agree to the suggested classifications (Skin. Sens 1, H317; STOT RE 2, H373, Aquatic Acute 1, H400, and Aquatic Chronic 1, H410). However we would like the proposing MSCA to consider classification for reproductive toxicity 2 (see comments below).

Dossier Submitter's Response

Comment has been considered in the response to the general comment number 1

RAC's response

The data on reproductive toxicity has been carefully review by the RAC. See further comments on reproductive toxicity in that section below.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26/06/2012	France	BCS	Company-Manufacturer / Germany	6

Comment received

Page 54 - Summary and conclusion on carcinogenicity. Please consider the following.
Squamous cell carcinomas of the cornea in male rats at the highest doses tested (200 and 800ppm, equivalent to approximately 8.3 and 32 mg/kg bw/day) in the chronic male rat toxicity/carcinogenicity study are triggered by eye keratitis and inflammation due to tyrosine accumulation.
Tembotrione is a very strong HPPDase inhibitor and in the male rat already provokes systemic increase and accumulation of tyrosine above the threshold of 1000 nmol/L in the male rat at 6 ppm (equivalent to approximately 0.3 mg/kg bw/day)
At plasma tyrosine concentrations greater than the threshold level of approximately 1000 nmol/mL, rats develop ocular lesions in the eye, which are manifest as stellate shaped corneal opacities.

Additionally, an inflammatory process is induced in the cornea which leads to degeneration/necrosis and regeneration/proliferation in the corneal epithelium. It is well established that persistent regenerative cell replication with an epithelium can lead to squamous cell carcinoma. These types of eye lesions did not occur in mice and, due to the similarity of tyrosine catabolism between mice and humans, cannot occur in humans as well.

Dossier Submitter's Response

Comment noted

RAC's response

This endpoint has not been evaluated by the RAC.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
26/06/2012	France	BCS	Company-Manufacturer / Germany	7

Comment received

Page. 86 - Summary and discussion of reproductive toxicity. Please consider the following. In the rabbit teratology study with tembotrione visceral examination of the foetal head revealed slightly dilated cerebral ventricles in three foetuses from two dams of the highest dose level of 100 mg/kg bw/day which provoked severe maternal toxicity (mortality and marked decreased body weight). Two of the three foetuses were quite small and weighed about 33-34 g. The visceral evaluation of the head was performed after fixation in Bouin's solution, a technique that can provoke artificial shrinkage, especially when sectioning small brain. This hypothesis is supported by comparison of the photos of the brain of the three foetuses of the high dose groups with those of the controls. The photos confirm that the dilation of the cerebral ventricle is very subtle and the difference with control barely perceptible. There were no other malformations or anomalies on the CNS or findings showing a perturbation of the cerebrospinal flux (i.e. hydrocephaly or spina bifida) in any of the treated groups which would support a treatment-related effect on the cerebral ventricles. Therefore, after observation of the slides, the PRAPER meeting concluded that no classification for developmental toxicity is required.

Dossier Submitter's Response

Comment noted

RAC's response

We agree that the 20% dam mortality at the highest dose is a cause for concern when evaluating the study, and that those effects noted at the top dose (100 mg/kg/day) could be caused by maternal toxicity and therefore should not be considered for classification. However, tembotrione affects skeletal development in rats (variations) and rabbits (anomalies and variations), and decreases pre- and postnatal growth rates in rats, at doses not affecting e.g. maternal body weights or survival of the dams. The MoA is likely to be tyrosinaemia, leading to effects characterised by a decreased growth rate of the pups. RAC is of the opinion that human relevance of this MoA has to be assumed, even though we acknowledge big species differences in sensitivity. The RAC therefore concludes classification for developmental toxicity as Cat 2 H361d (CLP) is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
28/06/2012	France		MSCA	8

Comment received

p 79 (4.11.3 developmental rabbits) and p 85 (4.11.5 Summary and discussion of reproductive toxicity)

Skeletal observations clearly showed a dose-related increase in some foetal delayed ossification and anomalies on ribs and vertebrae at 10 and 100 mg/kg /day. Their frequencies were higher than the historical controls. Furthermore maternal toxicity occurred only at 100 mg/kg /day. A relation could be established between hypertyrosinemia and foetal skeletal effects. Therefore a classification and labelling Repr. Cat.3 R 63: "possible risk of harm to unborn child" according to 67/548/CE directive and Repr. Cat.2 H361d: "suspected of damaging the unborn child" according to regulation (EC) No 1272/2008 can be proposed for reproduction.

Dossier Submitter's Response

Developmental toxicity study in the rabbit by gavage (Wason S, 2003b), and

Position paper: Tembotrione: Rabbit teratology (Mallyon B, Semino G, 2006)

100mg/kg bw/day:
Maternal effects: Severe maternal toxicity (5 deaths/sacrifices between gestation days 15 and 22), reduced food consumption, up to -43% decreased body weight change)
Foetal Effects:
- Variations above HCI: incomplete ossification of hyoid centrum, atlas centrum, 1st and 2nd sternebrae, hindpaws, and pubis; extra ossification site between atlas and axis
- Anomalies above HCI: Dilated cerebral ventricles; 1st and 2nd sternebrae unossified, extra sternebral ossification, cartilage of 8th rib attached to sternum, 1st rib short, cartilage of 1st rib not attached to sternum, cartilage of 1st and 2nd rib fused, presence of 27 pre-sacral vertebrae, 13 thoracis rib(s) and 27 pre-sacral vertebrae

10 mg/kg bw/day:
Maternal effects: No mortality, but clinical signs and reduced food consumption (-17% from GD6-8). One animal aborted and was subsequently necropsied.
Foetal Effects:
- Variations above HCI: incomplete ossification of atlas centrum, 1st and 2nd sternebrae, and pubis; extra ossification site between atlas and axis
- Anomalies above HCI: 1st and 2nd sternebrae unossified, extra sternebral ossification, cartilage of 8th rib attached to sternum, 1st rib short, cartilage of 1st rib not attached to sternum, cartilage of 1st and 2nd rib fused, presence of 27 pre-sacral vertebrae, 13 thoracic ribs and 27 pre-sacral vertebrae

Pregnant rabbits receiving 10mg/kg bw/day tembotrione from GD6-28 had markedly higher blood tyrosine levels (up to 7-fold increase compared to control animals).

Studies conducted with other HPPDase inhibitors (Isoxafluole, Sulcotrione, Mesotrione) have provoked similar effects (delays in ossification, presence of 27 pre-sacral vertebrae and 13th thoracic ribs).

The finding 'dilated cerebral ventricles' is most likely due to preparation techniques (difficulties with sectioning, artificial shrinkage). The severity of this finding is very low, and in absence of other parameters showing a disturbed cerebrospinal flux, not considered sufficient to warrant classification (see also comment number 7 by the notifier).

RAC's response

Tembotrione affects skeletal development in rats (variations) and rabbits (anomalies and variations), and decrease pre- and postnatal growth rates in rats, at doses not affecting e.g. maternal body weights. The MoA is likely to be tyrosinaemia, leading to effects characterised by a decreased growth rate of the pups. Since this MoA is relevant for humans, the RAC concludes classification for developmental toxicity as Cat 2 H361d (CLP) is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
29/06/2012	Sweden		MSCA	9

Comment received

The description of maternal toxicity could be somewhat clearer; the tables on body weight are not convincing (e.g. Table 25, 56 and 61) – an article about maternal toxicity can be found at Birth Defects Res B Dev Reprod Toxicol. 2011 Feb; 92(1):36-51.

Page 75, point 6. Decreased numbers of corpora lutea in the ovary – unusual finding – this could be a sign of an effect with future consequences for reproduction. What is the relevance in relation to human reproduction of such an effect?

Page 77-79 Developmental toxicity study in rats (Watson, 2003a): Maternal toxicity as presented is not convincing enough to dismiss the dose-dependent and relatively large increase in skeletal variations and anomalies.
Page 79- 84 Developmental toxicity, rabbit (Wason, 2003b): Also here the maternal toxicity is not presented convincing enough to dismiss the findings. A dose dependent increase in litter incidence of skeletal anomalies over the two highest doses of e.g. unossification of 1st and 2nd sternebrae, cartilage of the 8th rib being attached to the sternum, cartilage of 1st and 2nd rib fused, presence of

27 presacral vertebrae (Table 63). To support this, there are also dose related increases in variations (Table 62) over all three doses. Several of these findings also exceed the historical controls in the 2 highest doses (Table 65).

Page 88 and 93 Developmental neurotoxicity: The finding of decrease in acoustic startle at the mid- and high dose levels – why is this not considered a significant developmental toxicological finding?

Dossier Submitter's Response

Two generation reproductive toxicity in the rat (Young, Fickbohm, 2005) and Position paper: Tembotrione: two generation reproductive study in the rat (Semino, 2006):

The number of corpora lutea was statistically significantly decreased at 1500 ppm. There were no ovarian weight differences or evidence of other reproductive effects or problems, such as oestrus cyclicity, pregnancy rate, number of implantation sites, or organ histopathology. According to "An Evaluation and Interpretation of Reproductive Endpoints for Human Health Risk Assessment" (Daston GP and Kimmel CA, 57-74; 1999), the sole reduction of corpora lutea is not considered to be an adverse effect.

Developmental toxicity study in the rat by gavage (Wason, 2003a), Effect of tyrosinaemia on pregnancy and embryo-foetal development in the rat (Kennel, 2006), and Position paper: Tyrosinaemia and developmental effects (Semino, 2009):

In several standard rat developmental studies conducted with HPPDase inhibitors, the following findings were consistently observed: reduced foetal weight, general delay in ossification, increased incidence of short 14th rib or extra ossification points on the 14th thoracic vertebra. In the rabbit, the main skeletal finding was presence of 13th rib and 17 pre-sacral vertebrae.

Elevated plasma tyrosine levels during pregnancy were measured in both species (Repetto 2008 and 2009, discussed in the position paper cited above).

In a special study conducted with NTBC (another HPPDase inhibitor), elevated dietary tyrosine levels, and combinations of these 2 factors (Kennel 2006), the same findings were provoked by elevated tyrosine levels alone, by NTBC alone, and aggravated by the combination (for details, please see position paper).

In a developmental study with mice conducted with mesotrione, which do not accumulate tyrosine in the plasma after HPPDase inhibition, no such effects were observed.

We therefore conclude that the foetal effects are not due to the compound tembotrione itself but are secondary to the elevated plasma tyrosine levels.

Developmental toxicity study in the rabbit by gavage (Wason, 2003a):
Considered in the response to comment number 8

Developmental neurotoxicity in rats (Sheets, Gilmore, and Hoss 2005):
The effect was observed in one sex only and only on GD60, not on GD22. Dose-response relationship was absent (the effect was slightly more pronounced at 200ppm compared to 1500ppm). The other parameter observed (Latency to peak) was unchanged. At the 2 highest dose levels, the reduction in mean body weight compared to control animals was -11,6% (200ppm) and -8,5%(1500ppm) on GD60. In the absence of any other neurotoxicological findings, this effect was considered incidental.

RAC's response

Tembotrione affects skeletal development in rats (variations) and rabbits (anomalies and variations), and decreases pre- and postnatal growth rates in rats, at doses not affecting e.g. maternal body weights. The MoA is likely to be tyrosinaemia, leading to effects characterised by a decreased growth rate of the pups. RAC is of the opinion that human relevance of this MoA has to be assumed, even though we acknowledge big species differences in sensitivity. RAC therefore concludes classification for developmental toxicity as Repr. 2 H361d (CLP) is warranted. Concerning the corpora lutea, the RAC is of the opinion that a reduced number of corpora lutea can be an adverse finding, but that this isolated finding, in successfully reproducing animals, is not sufficient reason for classification for effects on fertility.

OTHER HAZARDS AND ENDPOINTS

Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
25/06/2012	Germany		MSCA	10
Comment received				
DE agrees with the proposed classification Skin Sens. 1B, H317 for tembotrione.				
Dossier Submitter's Response				
Comment noted, considered in response to general comment number 1				
RAC's response				
Strictly based on the data (100% response at 2.5% tembotrione), 1B is appropriate. However, had lower concentrations been tested, it cannot be excluded that >60% of the animals would respond at a concentration of 1%, making it difficult to rule out a higher potency (Cat. 1A). The RAC is therefore of the opinion that category 1, without defining the sub-category is the correct classification.				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
28/06/2012	Denmark		MSCA	11
Comment received				
As suggested on page 39 in the CLH report the substance should be classified as a skin sensitizer in subcategory 1B in accordance with the 2.nd ATP to CLP. This should also be evident in table 2, page 7, showing the proposed harmonised classification. Regarding the Guinea pig skin sensitization study, we believe that the test guideline corresponds to OECD 406 (and not OECD 404, as stated on p. 37)				
Dossier Submitter's Response				
Comment noted, considered in response to general comment number 1				
RAC's response				
See the RAC response to comment no. 10				

Specific target organ toxicity – repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
25/06/2012	Germany		MSCA	12
Comment received				
DE agrees with the proposed classification STOT RE2, H373 for tembotrione due to mortality observed in pregnant rabbits at 100 mg/kg bw/day (developmental toxicity study).				
Dossier Submitter's Response				
According to 1272/2008, for the standard animal studies in rats or mice that provide information about classification as STOT are 28 day, 90 day or lifetime studies (up to 2 years). Data from repeat dose studies performed in other species shall also be used, if available. Other long-term exposure studies, such as studies on reproductive toxicity, may also provide evidence. A wide variety of studies conducted in mice, rats, rabbits, and dogs are available. Classification based on effects on cornea observed in rats and dogs is not considered appropriate, as the effect is considered species-specific with little relevance to humans. The proposal for classification and labeling was based on severe maternal toxicity (5 deaths) in the developmental toxicity study in rabbits at 100mg/kg bw/day. The deaths occurred between gestation days 15 and 22, dosing began at GD 6. The guidance values given in regulation (EC) 1272/2008 for STOT repeated exposure are 10-100mg/kg bw/day for rats in a 90-day study via oral exposure.				

Due to the severity and irreversibility of the finding, and due to the fact that the deaths occurred after relatively few doses, STOT RE 2 was considered justified by the majority of the PRAPeR experts.

RAC's response

Because of the 20 % mortality in the rabbit study, RAC supports classification with STOT RE 2. Additionally, the findings of eye, kidney and liver toxicity in rats fulfil the criteria for classification with STOT RE 2. The following hazard phrase is proposed; May cause damage to the eye, kidney and liver through prolonged or repeated exposure.

Date	Country	Organisation	Type of Organisation	Comment number
28/06/2012	United Kingdom	HSE UKCA	MSCA	13

Comment received

We would question whether the mortality observed in pregnant rabbits at 100 mg/kg/day (Wason, S; 2003b) support classification with R48/STOT-RE as currently outlined in the report. We suggest that further consideration is given to the available repeat dose and chronic toxicity data in order to conclude on this hazard class.

Dossier Submitter's Response

Comment noted, considered in response to comment number 12

RAC's response

16 repeated dose toxicity studies are indeed available, but repeated dose toxicity data in rabbits could only be sourced from a developmental toxicity study in that species. Out of 25 dams administered 100 mg/kg/day in a developmental toxicity study, 5 dams died prematurely between gestation day 15 and 22. The effect is unexpected considering the short exposure time (10-17 days). However, mortality was also observed in males of the 90 days dog study at 250 mg/kg/day and in males of the 2 year study at 280 mg/kg/day. As no other studies are available in rabbits, it has to be assumed that the rabbit mortality can be explained by a very high sensitivity. The rabbit mortality is clearly severe and occurs below the guidance value for a 28 days study, thus warranting classification with STOT RE 2 (H373). The proposal of the dossier submitter is thus supported by RAC. Additionally, the findings of eye, kidney and liver toxicity in rats fulfil the criteria for classification with STOT RE 2. The following hazard phrase is proposed; May cause damage to the eye, kidney and liver through prolonged or repeated exposure.

Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
25/06/2012	Belgium		MSCA	14

Comment received

Based on the results of the aquatic toxicity test, the fact that the substance is not rapidly biodegradable and that the substance shows low potential to bioaccumulate, it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic acute 1, H400 and Aquatic chronic 1, H410.

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, tembotrione should be classified as N, R50/53.

We agree partially with the proposed classification by the Austrian CA. Concerning the settings of the M-factors we agree with the chronic M-factor of 10 based on the 7dNOErC Lemna gibba = 2,4µg/l and the fact that the substance is not rapidly degradable. However we believe that the acute M-factor should be 100 instead of 10. The study on Lemna gibba(Sowig, 2003) is considered valid and showing that Lemna gibba is the most sensitive species for acute toxicity with an 7d ErC50 of =8,48µg/l.

Dossier Submitter's Response

We agree with the Belgian authorities to use the most sensitive endpoint (*Lemna gibba; S*owig, 2003) for acute classification. Tembotrione is of high acute toxicity to *Lemna gibba* (Sowig, 2003) with an 7d ErC50 of =8,48 µg/l and fulfills the criteria for the proposed classification as R50 according to Directive 67/548/EEC and the criteria for the proposed classification as H400 according

to Regulation EC 1272/2008. A M-factor of 100 is applicable based on 0.001 < L(E)C50 ≤ 0.01 mg/L

Summary and discussion: Acute (short-term) aquatic toxicity

Data element: Acute (short-term) aquatic toxicity Generally expressed in terms of LC_{50} or EC_{50} (mg/L)					
	$L(E)C_{50}$ [mg/L]		Test guideline / design	GLP (y/n)	Reliability *
Fish (96 hr LC_{50}):					
Oncorhynchus mykiss	> 100		US-EPA OPPTS 850.1075, OECD 203	y	
Lepomis acrochirus	> 100		US-EPA OPPTS 850.1075, OECD 203	y	
Cyprinodon variegatus	> 100		US-EPA OPPTS 850.1075	y	
Crustacea (48 hr EC_{50}):					
Daphnia magna	*49.8*		OECD 202, US-EPA 72-2	y	
Algae/aquatic plants (72 or 96 hr E_rC_{50}):					
Pseudokirch.subcapitata	Biomass Growth rate	0.38 0.75	OECD 201, US-EPA J § 123-2, EU C.3	y	
Anabaena flos-aquae	Biomass (96 h) Growth rate (72 h)	64 71	OECD 201, US-EPA J § 123-2, EU C.3		
Navicula pelliculosa	Biomass Growth rate	10.8 47.9	OECD 201, US-EPA J § 123-2, EU C.3		
Skeletonema costatum	Biomass Growth rate	5.1 4.5	OECD 201, OPPTS 850.5400, EU C.3	y	
Lemna gibba	Biomass Growth rate	0.00599 **0.00848**	OECD draft 1998, US-EPA J § 123-2	y	
Other aquatic organisms (including sediment)					
Marine *invertebrate* (96 hr E/LC_{50}):					
Americamysis bahia	**Mortality** Subl. effects	0.1	US EPA 72-3, OPPTS 850.1035 (draft)	Y	
Crassostrea virginica	Shell growth	14	US EPA 72-3, OPPTS 850.1025 (draft)		
Conclusion: **Classification follows from the toxicity to the most sensitive species *Lemna Gibba* with an ErC50 = 0.00848 mg/L, (Sowig, 2003)**					

Comparison with criteria for environmental hazards

Endpoint	**Classifcation Criteria (criteria in bold)**		**Evidence for Tembotrione**
	CLP (2nd ATP)	**DSD**	
Degradation Tembotrione	Tembotrione is hydrolytically stable at environmentally relevant pH values from pH 4 to pH 9. Photodegradation of Tembotrione was moderate with an experimental half-life of 56.3 days under the test conditions. Tembotrione is not readily biodegradable, and does not meet the criterion for rapid degradation in a water/sediment study with a DT50 whole system of 108 days. Based on available data a non rapid degradation is proposed for tembotrione.		The classification as **R53** according to Directive 67/548/EEC. is based on the fact that the active substance is **not considered as ready biodegradable/rapid degradable.**

<table>
<tr><td>Bioaccumulation Tembotrione</td><td colspan="2">Log K_{ow} is < 4
Tembotrione Log K_{ow} = -1.09
at pH 7 and 24 °C</td><td>Log K_{ow} is < 3
Tembotrione Log K_{ow} = -1.09
at pH 7 and 24 °C</td><td>The measured log POW is -1.09 (at pH 7 and 24 °C) and is below the two classification criteria of 3 and 4, therefore Tembotrione is considered to have a low bioaccumulation potential.</td></tr>
<tr><td rowspan="2">Acute aquatic toxicity Tembotrione</td><td colspan="3">0.001 < LC50 ≤ 0.01 mg/L</td><td rowspan="2">Tembotrione is of high acute toxicity to Lemna gibba with an ErC50 = 0.00848 mg/L and fulfills the criteria for the proposed classification as R50 according to Directive 67/548/EEC and the criteria for the proposed classification as H400 according to Regulation EC 1272/2008. A M-factor of 100 is applicable based on 0.001 < L(E)C50 ≤ 0.01 mg/L</td></tr>
<tr><td colspan="3">Lemna gibba with an ErC50 = 0.00848 mg/L, (Sowig, 2003)</td></tr>
<tr><td rowspan="2">Chronic aquatic toxicity Tembotrione</td><td colspan="2">For non rapidly degradable substances:
0.001 <NOEC ≤0.01 mg/l</td><td rowspan="2"></td><td rowspan="2">Tembotrione is of high chronic toxicity to water plants (Lemna gibba) with a $NOEC_{GROWTH\ RATE}$ = 0.0024mg/L. Therefore Tembotrione fulfills the criteria for the proposed classification as H410 according to Regulation EC 1272/2008. A M-factor of 10 is applicable based on 0.001 < NOEC ≤ 0,01mg/l (no rapid degradation).</td></tr>
<tr><td>Lemna gibba</td><td>NOEC(7 d) = 0.0024 mg/L</td></tr>
<tr><td rowspan="5">SUMMARY</td><td colspan="2" rowspan="5">H400 M-factor =100
H410 M-factor =10</td><td colspan="2">R50/53</td><td rowspan="5">PROPOSED CLASSIFICATION</td></tr>
<tr><td>Classification</td><td>Concentration [in %]</td></tr>
<tr><td>N, R50/53</td><td>≥ 0.25</td></tr>
<tr><td>N, R51/53</td><td>≥ 0.025 - < 0.25</td></tr>
<tr><td>R52/53</td><td>≥ 0.0025 - < 0.025</td></tr>
</table>

Conclusion of environmental classification and labelling according to Directive 67/548/EEC

Conclusion of environmental classification according to Directive 67/548/EEC

N Dangerous for the Environment

R50 Very toxic to aquatic organisms

R53 May cause long term effects in the environment

SCLs

Classification	Concentration* [in %]
N, R50/53	≥ 0.25
N, R51/53	≥ 0.025 - < 0.25
R52/53	≥ 0.0025 - < 0.025

*concentration of Tembotrione in the preparation

Conclusion of environmental classification according to Regulation EC 286/2011 (2nd ATP to EC 1272/2008)

Classification categories	aquatic environmental hazard **acute category 1** aquatic environmental hazard **chronic category 1**
GHS Pictogram	
Signal Word	Warning
Hazard Statement	'Very toxic to aquatic life', 'Very toxic to aquatic life with long lasting effects'EUH401
M-factor (acute)	100
M-factor (chronic)	10

RAC's response

We agree with the MS's comments. The acute toxicity category should be based in the lowest ErC50 of 0.0084 mg/l which corresponds to *Lemna gibba,* this value is < 1 mg/l, therefore tembotrine should be classified in Aquatic Acute category 1 (H400), with a M-factor of 100, because the EC50 is between 0.001 and 0.01 mg/l.

Date	Country	Organisation	Type of Organisation	Comment number
25/06/2012	Germany		MSCA	15

Comment received

P. 141 Summary and discussion: Acute (short-term) aquatic toxicity: we do not agree with the selected Endpoint used for classification. According to the information given, Lemna gibba is the most sensitive species with ErC50 = 0.00848 mg/L (Sowig P. (2003)). We suggest using this endpoint with a classification as H400 according to Regulation EC 1272/2008 and M-factor (acute) of 100.

Dossier Submitter's Response

We agree with the German authorities to use the most sensitive endpoint (*Lemna gibba;* Sowig, 2003) for acute classification. Tembotrione is of high acute toxicity to *Lemna gibba* (Sowig, 2003) with an 7d ErC50 of =8,48µg/l and fulfills the criteria for the proposed classification as R50 according to Directive 67/548/EEC and the criteria for the proposed classification as H400 according to Regulation EC 1272/2008. A M-factor of 100 is applicable based on 0.001 < L(E)C50 ≤ 0.01 mg/L.
For more information see above (response to the comment of Belgian authorities)

RAC's response

Please see the RAC's response to comment no. 14.

Date	Country	Organisation	Type of Organisation	Comment number
28/06/2012	United Kingdom	HSE UKCA	MSCA	16

Comment received

Please can the Austrian CA clarify if the NOErC quoted for the Lemna Growth inhibition test referenced as Dogerloh 2004a is 14 day (Table 5.5 of the proposal) or 7 day (section 5.4.3, pages 133-134 of the proposal)? In addition, we suggest that the ErC50 based on measured data from this study should be included for comparison with the Sowig (2003) study.
We disagree that the acute classification should be based on the Americamysis bahia EC50 of 0.1 mg/l as the Lemna data suggest these taxa are more sensitive with lower EC50 values. This will

affect the acute M-factor and SCLs.

Dossier Submitter's Response

The study duration time of Lemna Growth inhibition test referenced as Dogerloh 2004a is 7 days (Table 5.5 of the proposal). This was considered above in the response to the comment of Belgian authorities.

As noted on page 134 – 135 the study author(s) (Dogerloh 2004a) based the EC50 on nominal concentrations (test concentrations in the water phase were between 61 and 73 % of nominal and hence below 80 % at test end). The RMS (CA) asked the notifier to re-calculate the EC50 values based on mean measured concentrations. The notifier did not submit revised EC50 values until the finalisation of the revised DAR, so the available test (Sowig, 2003) was used for classification.

We agree with the English authorities to use the most sensitive endpoint (*Lemna gibba;* Sowig, 2003) for acute classification. Tembotrione is of high acute toxicity to *Lemna gibba* (Sowig, 2003) with an 7d ErC50 of =8,48µg/l and fulfills the criteria for the proposed classification as R50 according to Directive 67/548/EEC and the criteria for the proposed classification as H400 according to Regulation EC 1272/2008. A M-factor of 100 is applicable based on 0.001 < L(E)C50 ≤ 0.01 mg/L.
For more information see above (response to the comment of Belgian authorities)

RAC's response

Please see the RAC's response to comment no. 14.

Date	Country	Organisation	Type of Organisation	Comment number
28/06/2012	France		MSCA	17

Comment received

P143: There is a typographic error concerning the log Kow. Based on the table 84 (p 112), the log Pow is -1.09 at pH = 7 and 24 °C (instead of 1.09).

P141/143: Could you explain why the classification proposal for acute is based on the LC50 of Americamysis bahia (LC50 = 0.1 mg/L)? Indeed, a lower toxicity value is available with Lemna gibba (ErC50 = 0.00848 mg/L). Based on this lower toxicity value, the classification proposal for acute could be Aquatic acute 1 H400 with a M-factor = 100.

P142/143: Could you confirm that a study performed with sediment can be used for the classification? If no, the NOEC of 0.0032 mg/L from the study on Lemna gibba performed without sediment should be used. However, the classification proposal for chronic (Aquatic chronic 1 H410 with a M-factor = 10) will be not modified.

Dossier Submitter's Response

P143: The typo was considered above in the response to the comment of Belgian authorities.

P141/143: We agree with the French authorities to use the most sensitive endpoint (*Lemna gibba*; Sowig, 2003) for acute classification. Tembotrione is of high acute toxicity to *Lemna gibba* (Sowig, 2003) with an 7d ErC50 of =8,48µg/l and fulfills the criteria for the proposed classification as R50 according to Directive 67/548/EEC and the criteria for the proposed classification as H400 according to Regulation EC 1272/2008. A M-factor of 100 is applicable based on 0.001 < L(E)C50 ≤ 0.01 mg/L. For more information see above (response to the comment of Belgian authorities).

P142/143: We think this should be discussed by ECHA experts.

RAC's response

P141/143: Please see the RAC's response to comment no. 14.

P142/143: Regarding chronic toxicity, the lowest NOErC value corresponds to a study on *Lemna gibba* based on OCDE 221 (NOErC: 0.0024mg/l) however there is a modified exposure with sediment

present in the test system which can modify the toxicity, therefore the NOEC of 0.0032 mg/L from the study on *Lemna gibba* performed without sediment should be used. Nevertheless, the classification proposal for chronic category will not be modified. Taking into account NOEC value of 0.0032 mg/L and its no rapid degradation, tembotrine classifies as Chronic category 1 (H410) with a M-Factor of 10, because the NOEC value is between 0.001 and 0.01 and it is considered a no rapidly degradable substance.

Date	Country	Organisation	Type of Organisation	Comment number
29/06/2012	Sweden		MSCA	18

Comment received

We agree with that the substance is not rapidly biodegradable and has a low bioaccumulation potential. Regarding the toxicity of the substance we agree that based on the data available, tembotrione should be classified for both acute and chronic hazard according to CLP criteria. However, we would like to get more explanation as to why data on Americamysis bahia were chosen as a basis for derivation of M factor acute. Since the substance is herbicide and the toxicity data available clearly indicate that Lemna gibba is the most sensitive species, it seems reasonable to use these results for derivation of the acute M factor. We find the 14-day Lemna gibba study as valid (cf I.2.3.2. CLP Guidance) and, according to our understanding, data from this study should be used and the M factor adjusted accordingly.

Dossier Submitter's Response

We agree with the Swedish authorities to use the most sensitive endpoint (*Lemna gibba*; Sowig, 2003) for acute classification. Tembotrione is of high acute toxicity to *Lemna gibba* (Sowig, 2003) with an 7d ErC50 of =8,48µg/l and fulfills the criteria for the proposed classification as R50 according to Directive 67/548/EEC and the criteria for the proposed classification as H400 according to Regulation EC 1272/2008. A M-factor of 100 is applicable based on $0.001 < L(E)C50 \leq 0.01$ mg/L.
For more information see above (response to the comment of Belgian authorities).

RAC's response

Please see the RAC's response to comment no. 14.

Physical hazard

Date	Country	Organisation	Type of Organisation	Comment number
26/06/2012	France	BCS	Company-Manufacturer / Germany	19

Comment received

Page 7 With reference to Table 1: Substance identity The degree of purity is reported of 940 g/kg and the content of Toluene max. 10 g/kg.
BCS has the following comments to make
The values given for degree of purity of tembotrione and amount of the impurity toluene in the CLH document have been taken from the specification for the Pilot Plant Production of tembotrione
However, Tembotrione has been in full scale production since 2007, and the actual minimum content for the full scale production is specified as 945g/kg for tembotrione and max 2g/kg for the impurity toluene, as written in the Draft Assessment Report (revision 3 Nov 2011).

Dossier Submitter's Response

Noted

RAC's response

Noted

REFERENCES: None

ATTACHMENTS RECEIVED: None