Committee for Risk Assessment
RAC

Opinion
proposing harmonised classification and labelling
at EU level of
methyl 2,5-dichlorobenzoate

EC Number: 220-815-7
CAS Number: 2905-69-3

ECHA/RAC/CLH-O-0000003156-78-01/F

Adopted
28 November 2012

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CLH-O-0000003156-78-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: Methyl 2,5-dichlorobenzoate

EC No.: 220-815-7

CAS No.: 2905-69-3

The proposal was submitted by **Germany** and received by the RAC on **11/08/2011.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification:

	CLP	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	-	-
Original proposal by dossier submitter for consideration by the RAC	Acute Tox. 4; H302 Aquatic Acute 1; H400 Aquatic Chronic 1; H410 M-factor = 1	Xn; R22 N, R50-53 Concentration Limits: C ≥ 25% N; R50-53 2.5% ≤ C < 25% N; R51-53 0.25% ≤ C < 2.5% R52-53
Amended proposal by dossier submitter for consideration by RAC following public consultation	Acute Tox. 4; H302 Aquatic Chronic 2; H411	Xn; R22 N; R51-53 Concentration Limits: N; R51-53: C ≥ 25% R52-53: 2.5% ≤ C < 25%
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed	Acute Tox. 4; H302 Aquatic Chronic 2; H411	Xn; R22 N; R51-53 Concentration Limits:

by dossier submitter		N; R51-53: C ≥ 25% R52-53: 2.5% ≤ C < 25% where C is the concentration of Methyl 2,5-dichlorobenzoate in the preparation

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **17/08/2011**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **01/10/2011**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Marja Pronk**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **28 November 2012** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF RAC

The RAC adopted the opinion that **Methyl 2,5-dichlorobenzoate** should be classified and labelled as follows:

Classification & Labelling in accordance with CLP:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
607-706-00-3	methyl 2,5-dichlorobenzoate	220-815-7	2905-69-3	Acute Tox. 4 STOT SE 3 Aquatic Chronic 2	H302 H336 H411	GHS07 GHS09 Wng	H302 H336 H411			

Classification & Labelling in accordance with DSD:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
607-706-00-3	methyl 2,5-dichlorobenzoate	220-815-7	2905-69-3	Xn; R22 N; R51-53	Xn; N R: 22-51/53 S: (2-)46-61		

SCIENTIFIC GROUNDS FOR THE OPINION

RAC GENERAL COMMENTS

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The acute oral toxicity of 2,5-DCBME was in the same order of magnitude in rats and mice. The acute oral LD_{50} was 1030 mg/kg bw in rats and 910 mg/kg bw in mice. Mortality was observed at ≥ 750 mg/kg bw in rats and at ≥ 700 mg/kg bw in mice. The acute dermal LD_{50} in rats was greater than 10.000 mg/kg bw. The acute inhalation toxicity in rats could not be determined because use of spray or dust was not feasible in the test.

Dossier submitter's comparison with criteria

Toxicological result	CLP criteria	DSD criteria
Oral LD_{50}, rat, males: 1175 mg/kg Oral LD_{50}, rat, females: 1030 mg/kg $LD_{50,}$ mouse: 910 mg/kg bw, males & females	Cat. 4: 300 < LD_{50} ≤ 2000 mg/kg (oral)	Harmful: LD_{50} per oral, rat: 200 < LD_{50} ≤ 2000 mg/kg
Inhalation LC_{50}, rat: Not determined (no spray or dust feasible)	-	-
Dermal $LD_{50,}$ rat: > 10.000 mg/kg	Cat. 4: 1000 < LD_{50} ≤ 2000 mg/kg (dermal)	Harmful: LD_{50} dermal, rat or rabbit: 400 < LD_{50} ≤ 2000 mg/kg

Dossier submitter's conclusions on classification and labelling
The acute oral toxicity of 2,5-DCBME meets the CLP and DSD criteria. Based on the results of the acute oral toxicity studies 2,5-DCBME should be classified as Acute Tox. 4 (H302) according to CLP and as harmful, Xn; R22 "Harmful if swallowed" according to DSD.

The results of the acute dermal toxicity studies do not meet the CLP or DSD criteria. Classification and labelling of 2,5-DCBME concerning acute dermal toxicity is not required.

There are no results of the acute inhalation toxicity study to compare with the CLP and DSD criteria. No conclusion can be drawn on classification of 2,5-DCBME for acute inhalation toxicity.

Assessment and comparison with the classification criteria

During public consultation, support was expressed for the proposal.

Based on a comparison of the available LD_{50} values in rats and mice with the criteria, RAC supports the conclusion of the dossier submitter that 2,5-DCBME should be classified for acute oral toxicity (with **Acute Tox. 4 – H302** (CLP) and **Xn; R22** (DSD)), but not

for acute dermal toxicity. In the absence of data, RAC agrees that no conclusion can be drawn on the classification of 2,5-DCBME for acute inhalation toxicity.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of Dossier submitter's proposal

There are no relevant data relating to the classification of 2,5-DCBME for specific target organ toxicity by single exposure.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Dossier submitter's conclusions on classification and labelling
Classification and labelling is not required.

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for specific target organ toxicity – single exposure. During public consultation, one member state suggested that the findings of sedation and coma in the acute oral toxicity studies should be discussed in the context of the criteria for STOT SE.

In response to this comment, the dossier submitter argued that since the CLP guidance (3.8.2.1.2) states that human data or inhalation studies should be considered for STOT SE 3 (narcotic effects), no classification is proposed because effects were observed in *oral* studies.

RAC notes that this interpretation of the guidance is not correct, as the specific section states *"Although classification in **Category 3** is primarily based on human data, if available, animal data can be included in the evaluation. These animal data on RTI (respiratory tract irritation) and NE (narcotic effects) will generally come from standard acute inhalation studies, although it is possible that narcosis could be observed in studies using other routes."*

The guidance indicates (3.8.2.2.2) that *'narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia'*. In the oral single dose studies, all these symptoms were observed in rats and/or mice, as was sedation and (in rats) coma, at dose levels also resulting in mortality. Severe, but transient, ataxia was also observed in a 2-week oral dose-range-finding study in rats following dosing with 900 mg/kg bw/d (starting 10 minutes after dosing and lasting for 4-6 hours), a dose level that is close to the oral LD_{50} value of approximately 1000 mg/kg bw. No such effect was observed in that study at the next lower dose of 300 mg/kg bw/d, or in a rat oral 28-day study at doses of 100, 300 and 900 mg/kg bw/d. The latter study, however, showed reduced mobility in the form of paralysis of the hind legs at 300 and 900 mg/kg bw/d (as well as increased incidence of impaired gait and wire manoeuver, decreased sensitivity to toe pinch and tail pinch, decreased hind leg splay and limb rotation, decreased spontaneous locomotion movements, and decreased grip strengths of the fore and hind limbs, following a neurological assessment in week 4). The paralysis of the hind legs was seen from day 1 of treatment at 900 mg/kg bw/d, and from day 4 at 300 mg/kg bw/d. At both doses the effect was transient, lasting from 10 minutes to 6 hours after each dosing, and was no longer seen immediately after treatment was stopped on day 29.

From the available data it is clear that 2,5-DCBME is a neurotoxic substance, causing comparable effects in acute and repeated dose toxicity studies at doses that are within half an order of magnitude of each other. Looking at the onset and duration of the neurotoxic effects in the repeated dose studies, they do not seem more persistent than after acute exposure. Therefore, given their clearly transient nature, RAC considers the neurotoxic effects in the repeated dose studies to be indicative of acute toxicity (see also section 1.6.2 for further explanation).

The observed narcotic/neurotoxic effects in the oral acute and repeated dose toxicity studies fulfil the criteria for STOT SE 3. Whereas RAC notes that some of the effects occur at or near lethal dose levels, and for lethality the substance is already proposed to be classified, RAC does not consider additional classification for STOT SE to be a "double classification", given that some other effects (paralysis in particular) occur below lethal dose levels. RAC therefore proposes to classify 2,5-DCBME for specific target organ toxicity – single exposure (with **STOT SE 3 – H336**), in order to flag its narcotic/neurotoxic properties. No classification under DSD is warranted, as under DSD the corresponding R-phrase R67 is for vapours/inhalation route only.

RAC evaluation of skin corrosion/irritation

Summary of Dossier submitter's proposal

Corrosion

There is no evidence of skin corrosivity of 2,5-DCBME.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Dossier submitter's conclusions on classification and labelling
Classification and labelling is not required.

Irritation

Slight to moderate but transient signs of dermal irritation were noted after application to the skin of rabbits.

Dossier submitter's conclusions on classification and labelling
Slight to moderate but transient signs of dermal irritation were noted after application to the skin of rabbits. After 24 hours an erythema score of 1 was observed in 5/8 animals on the shaved skin. At 72 h and 7 d post application, all scores were 0. Oedema scores were 0 at all reading times. Since the mean values of the readings after 24 to 72 hours after application were below the thresholds defined in CLP and DSD, classification of 2,5-DCBME for skin irritation is not required.

Assessment and comparison with the classification criteria

Corrosion

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for corrosive properties. This proposal/endpoint was not specifically commented on during public consultation.

In the skin and eye irritation studies, no indications were found for a corrosive effect of 2,5-DCBME. RAC therefore supported the conclusion of the dossier submitter that 2,5-DCBME should not be classified for corrosivity.

Irritation

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for skin irritation. This proposal was not specifically commented on during public consultation.

In a skin irritation study with rabbits only slight, transient irritation was observed. For erythema, a maximum score of 1 was found in 5/8 animals after 24 h, both for intact and for abraded skin. At 72 h and 7 d post application, the scores for erythema were all 0. Oedema scores were 0 at all reading times. The mean score for erythema was below the threshold value of 2.3 for Skin Irrit. 2 – H315 (CLP) or 2 for Xi; R38 (DSD). RAC therefore supports the conclusion of the dossier submitter that 2,5-DCBME should not be classified for skin irritation.

RAC evaluation of eye corrosion/irritation

Summary of Dossier submitter's proposal

Slight to moderate but transient signs of ocular irritation were noted after application to the eyes of rabbits. In the eye irritation study, only a 10 % dilution of the substance was used. The authors of the study as well as the PRAPeR Expert Meeting (PRAPeR Expert Meeting 54 Sub-group 2 (07 – 11 July 2008) 11 July 2008, Dichlorobenzoic acid) proposed to classify the product containing 10 % of the test substance as "slightly irritant" as a precaution, because it could not be ruled out that the concentrate would not lead to stronger irritation to the eyes (EFSA 2008).

Dossier submitter's comparison with criteria
Up to 8 hours after the application, the conjunctiva showed redness, chemosis and secretion; 24 hours post application there was no evidence of irritation. The mean values of the readings after 24 to 72 hours after application were below the thresholds defined in CLP for Eye irritation, category 2 (positive response of corneal opacity ≥ 1 and/or iritis ≥ 1, and/or conjunctival redness ≥ 2 and/or conjunctival oedema (chemosis) ≥ 2; in at least in 2 of 3 tested animals, calculated as the mean scores following grading at 24, 48 and 72 h, and fully reversible within an observation period of 21 days); or Xi; R36, Irritating to eyes according to DSD (Significant ocular lesions within 72 h and persisting for at least 24 h, corneal opacity ≥ 2 but < 3, iris lesion ≥ 1 but < 1,5, redness of the conjunctivae ≥ 2,5, oedema of the conjunctivae (chemosis) ≥ 2).

Dossier submitter's conclusions on classification and labelling
Slight to moderate but transient signs of ocular irritation were noted after application of a 10 % dilution of 2,5-DCBME to the eyes of rabbits. The mean values of the readings after 24 to 72 hours after application were below the thresholds defined in CLP and DSD However, no conclusion can be drawn on the classification of 2,5-DCBME because only a 10 % dilution of 2,5-DCBME was tested.

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for eye irritation, in absence of data on 2,5-DCBME in a more concentrated form than 10%. During public consultation, support was expressed for the proposal.

In the eye irritation study with rabbits, a 10% solution of 2,5-DCBME caused slight to moderate and transient signs of ocular irritation. Conjunctival redness, chemosis and secretion (scores 1-3) was seen up to 8 h after application in all 8 animals tested, but scores for these effects were all 0 from 24 h up to 7 d post application. Methyl 2,5-dichlorobenzoate did not produce effects on the cornea or iris (scores 0 at all reading times). Based on these results, classification for eye irritation for a 10% solution of 2,5-

DCBME is not warranted. This conclusion was also drawn by EFSA in their peer review of 2,5-DCBME in 2008. Yet, as a precaution EFSA proposed to classify 2,5-DCBME for eye irritation with Xi; R36, because it could not be ruled out that a more concentrated form would not lead to a stronger irritation to the eyes. Rather than proposing a precautionary classification, RAC concludes that in the absence of appropriate data, no conclusion can be drawn on the classification for eye irritation.

RAC evaluation of Respiratory tract Irritation

Summary of Dossier submitter's proposal

There are no data relevant to the respiratory tract irritation classification.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Dossier submitter's conclusion on classification and labelling
No conclusion can be drawn on respiratory tract irritation.

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for respiratory tract irritation, due to a lack of data. This proposal/endpoint was not specifically commented on during public consultation.

In the absence of data, RAC agrees with the dossier submitter that no conclusion can be drawn on the classification for respiratory tract irritation.

RAC evaluation of skin sensitisation

Summary of Dossier submitter's proposal

In a maximisation test by Magnusson and Kligman no symptoms of skin sensitisation could be observed.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Conclusions on classification and labelling
Classification and labelling is not required.

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for skin sensitisation. During public consultation, this proposal/endpoint was not specifically commented on.

2,5-DCBME (0.1% at intradermal induction, 75% at topical application after treatment of skin with 10% sodium lauryl sulfate) tested negative in a guinea pig maximisation test according to Magnusson and Kligman. None of the animals (test and control) showed any skin reaction. RAC therefore supports the conclusion of the dossier submitter that 2,5-DCBME should not be classified for skin sensitisation.

RAC evaluation of respiratory sensitisation

Summary of Dossier submitter's proposal

There are no relevant data to discuss respiratory sensitisation.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Dossier submitter's conclusions on classification and labelling
No conclusion can be drawn on respiratory sensitisation potential.

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for respiratory sensitisation due to absence of data. During public consultation, this proposal/endpoint was not commented on.

In the absence of data, RAC agrees that no conclusion can be drawn on the classification for respiratory sensitisation.

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of Dossier submitter's proposal

The toxicity of 2,5-dichloro benzoic acid methylester was investigated in a 2-week dose-range finding study and a 28-day study, both in rats. In the 2-week study, administration of 900 mg 2,5-dichlorobenzoic acid methylester per kg bw/d caused severe ataxia in all animals starting 10 minutes after administration. The symptoms lasted for 4-6 h. The body weight was decreased relative to the controls. The food consumption was lower relative to the control group. The NOAEL of the study was 300 mg/kg bw/d.

In the 28-day study the test compound was administered once daily by gavage (7 d/week) at doses of 100, 300 and 900 mg/kg bw/d. Animals treated with 300 or 900 mg/kg bw/d showed reduced mobility in form of a paralysis of the hind legs. In addition, pilo-erection was noted in the high dose group. Animals treated with 300 or 900 mg/kg bw/d showed a dose-related increased incidence of impaired gait and wire manoeuvre, a decreased sensitivity to toe pinch and tail pinch, and a decreased hind leg splay and limb rotation. In addition, a dose-related significant decrease was noted for the slight and active movements of the spontaneous locomotion and in the grip strength of the fore and hind limbs. Male animals treated with 900 mg/kg bw/d showed a reduced body weight and effects on parameters of haematology and clinical chemistry. At 300 mg/kg bw/d, an increase in the relative liver weight was noted for the males. Animals treated with 900 mg/kg bw/d showed an increase in the organ weights of the liver of male and female animals and of kidneys of the female animals. Animals treated with 900 mg/kg bw/d revealed fatty infiltrations in the heart. Male animals showed an increased oligospermia in the epididymis. Body weight of the male animals did not normalise during the 6-week recovery period. The body weight remained 17 % below the control group. Other findings noted at the end of the treatment period had completely subsided at the end of the 6-week recovery period. The NOAEL of the 28-day study was 100 mg/kg bw/d.

There are no relevant findings in the 2-week and 28-day studies to discuss classification concerning specific target organ toxicity – repeated exposure (CLP) or repeated dose toxicity (DSD).

Dossier submitter's comparison with criteria

There are no relevant findings to compare with criteria for classification according to CLP or DSD.

Dossier submitter's conclusions on classification and labelling
There are no findings relevant for classification according to CLP or DSD.

Assessment and comparison with the classification criteria

During public consultation, one member state suggested that the findings of (seemingly transient) neurotoxic effects in the 28-day study should be discussed in the context of criteria and adjusted guidance values for STOT RE.

In response to this comment, the dossier submitter argued that the effects were fully reversible (i.e. signs of neurotoxicity occurred directly after gavage from day one onwards, and lasted from ten minutes to a few hours) and were not severe, and that therefore a classification for STOT RE is not proposed. The dossier submitter further argued that guidance values are not to be regarded as strict demarcation values.

In the 28-day toxicity study, neurotoxic effects were the most sensitive effects observed: they were observed at 300 and 900 mg/kg bw/d (reduced mobility in the form of paralysis of the hind legs and, following a neurological assessment in week 4, increased incidence of impaired gait and wire manoeuver, decreased sensitivity to toe pinch and tail pinch, decreased hind leg splay and limb rotation, decreased spontaneous locomotion movements, and decreased grip strengths of the fore- and hind limbs), whereas other effects were mainly noted at 900 mg/kg bw/d. The paralysis of the hind legs was transient, lasting 10 minutes to 6 hours after each dosing, and was no longer seen immediately after treatment was stopped on day 29. At 900 mg/kg bw/d it took one dose to manifest, but at 300 mg/kg bw/d four doses were necessary. Neurotoxicity (severe, but transient ataxia) was also seen in the 2-week dose-range finding study, but only at the highest dose of 900 mg/kg bw/d.

Given that at 300 mg/kg bw/d the paralysis took four days to manifest, RAC considered whether this was an indication of repeated dose toxicity, or whether it was in fact more a sign of acute toxicity. The latter possibility was raised because of the clearly transient nature of the paralysis and the fact that disturbances of coordination and other neurotoxic effects such as ataxia were also observed in the acute toxicity studies at only slightly higher (2.5-fold) doses of 2,5-DCBME.

After this issue had been raised by RAC, as further explanation of the nature of the neurotoxic effects observed, Industry referred to a WHO evaluation of (a.o.) benzoates and benzoic acid (WHO, 1997). In this evaluation, the toxic effects induced upon exposure to high doses of these substances are linked to glycine depletion. Benzoates are metabolised to benzoic acid, which in turn is conjugated with glycine to hippuric acid (=benzoylglycine). This conjugation is a saturable process in which the availability of glycine is the rate limiting step. Therefore, high doses result in glycine depletion leading to toxic effects, including neurotoxicity. Supplementation with glycine was shown to alleviate the toxic effects.

It was argued that the above explanation is consistent with findings in the 28-day study for 2,5-DCBME, the metabolism and elimination of which is rapid (within 24 h), without accumulation in organs/tissues, and for which the major metabolites have been identified as the free acid (2,5-dichlorobenzoic acid) and the glycine conjugate (2,5-dichlorobenzoylglycine). The high dose group (900 mg/kg bw, which is close to the LD_{50}) in the 28-day study showed effects from day 1 whereas the lower dose group (300 mg/kg bw) showed effects only after 4 days (after depletion of the glycine pool). The effects lasted only 10 minutes to 6 hours after application and all animals showed a total recovery from day 29 on when no further test substance was administered. Therefore, Industry is of the opinion that the (clearly severe) effects should be regarded as acute

toxicity on each single day because on each day after cessation of treatment, further recovery was observed. They consider a classification for STOT RE 2 not justified, as there are definitely no signs for repeated toxicity, given also the rapid metabolism and elimination and the absence of accumulation.

Based on an overall weight of evidence approach, taking into consideration the onset and duration of the paralysis (indicating that the neurotoxic effects in the repeated dose studies do not seem more persistent than after acute exposure), the likely cause of this (and other) neurotoxic effects, and the toxicokinetic profile of 2,5-DCBME, RAC concludes that the observed neurotoxicity in the 28-day study is acute in nature, thereby not warranting classification for STOT RE.

RAC evaluation of germ cell mutagenicity

Summary of Dossier submitter's proposal

2,5-DCBME was devoid of any mutagenic activity in in vitro and in vivo test systems.

Dossier submitter's comparison with criteria
The results of the in vitro as well as the in vivo studies demonstrated, that 2,5-DCBME has no mutagenic or clastogenic potential.

Dossier submitter's conclusions on classification and labelling
Classification and labelling is not required.

Assessment and comparison with the classification criteria

During public consultation, this proposal/endpoint was not commented on.

Given that, overall, 2,5-DCBME tested negative in three in vitro studies (a bacterial mutation assay, and a mammalian gene mutation and chromosomal aberration assay) and one in vivo study (a micronucleus assay), RAC supports the conclusion of the dossier submitter that 2,5-DCBME should not be classified for mutagenicity.

RAC evaluation of carcinogenicity

Summary of Dossier submitter's proposal

There are no data relevant to the carcinogenicity classification.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Dossier submitter's conclusions on classification and labelling
No conclusion can be drawn on classification and labelling.

Assessment and comparison with the classification criteria

During public consultation, this proposal/endpoint was not commented on.

In the absence of data, RAC agrees that no conclusion can be drawn on the classification for carcinogenicity.

RAC evaluation of reproductive toxicity

Summary of Dossier submitter's proposal

There are no relevant data to discuss.

Dossier submitter's comparison with criteria
There are no relevant data to compare with criteria.

Dossier submitter's conclusions on classification and labelling
No conclusion can be drawn on classification and labelling.

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter not to classify 2,5-DCBME for reproductive toxicity due to absence of data. During public consultation, this proposal/endpoint was not commented on.

RAC noted that in a rat oral 28-day study, oligospermia in the epididymes was observed in 5 out of 10 males dosed with 900 mg/kg bw/d. No other effects on the testes were reported. In the absence of more detailed information on e.g. the degree of the reduction in sperm concentration, it is difficult to judge whether this effect, which was apparently no longer found after a 6-week recovery period, is of toxicological significance.

In the absence of appropriate data, RAC agrees that no conclusion can be drawn on the classification for reproductive toxicity.

RAC evaluation of physico-chemical properties

Summary of Dossier submitter's proposal

Due to the physico-chemical properties of 2,5-DCBME, a classification is not necessary for this endpoint (data conclusive, but not sufficient for classification).

Assessment and comparison with the classification criteria

Although originally not addressed, following a comment during public consultation the dossier submitter stated that the available data indicate that a classification for physico-chemical properties is not necessary. RAC supports the non-classification for physico-chemical properties, as 2,5-DCBME is not explosive, not flammable, has no self-ignition up to the melting point and has no oxidising properties.

RAC evaluation of environmental hazards

Summary of Dossier submitter's proposal

Dossier submitter's comparison with criteria
In aquatic toxicity studies, an acute EC_{50} value for aquatic invertebrates was obtained at a nominal 2,5-DCBME concentration of 7.5 mg/l. The actual concentration of test substance over the test duration was not determined. There are no results of long-term toxicity studies for algae, invertebrates, fish and sediment dwelling organisms.

There are no data (screening or simulation tests) to assess whether 2,5-DCBME is readily biodegradable or not. Considering the results of hydrolysis and photolysis, 2,5-DCBME is

considered not rapidly biodegradable (i.e. does not meet the criterion of >70% degradation within 28 days) for the purposes of classification and labelling.

2,5-DCBME has a log Kow of 3.46. There are no experimentally derived BCF values. The log Kow is above the trigger of 3 (criterion for bioaccumulating potential according to DSD), but is not above the trigger of 4 (criterion for bioaccumulating potential according to CLP).

Dossier submitter's conclusion on classification and labelling according to CLP
Methyl 2,5-dichlorobenzoate fulfils the criteria for classification as aquatic environmental hazard chronic category 2, H411 based on the lowest nominal acute toxicity data for Daphnia magna (EC_{50} = 7.5 mg/l) in a 48-h static study.

Dossier submitter's conclusions on classification and labelling according to DSD
Methyl 2,5-dichlorobenzoate fulfils the criteria for classification with N; R51-53.

Based on the lowest nominal toxicity data for *Daphnia magna* (EC50 = 7.5 mg/l) in a 48-h static study the following specific concentration limits should be applied:

Concentration	Classification
C ≥ 25%	N; R51-53
2.5% ≤ C < 25%	R52-53

where C is the concentration of Methyl 2,5-dichlorobenzoate in the preparation

Assessment and comparison with the classification criteria

The evaluation by RAC relates to the proposal of the dossier submitter to classify 2,5-DCBME for aquatic chronic toxicity. Originally, the dossier submitter proposed to classify the substance for both aquatic acute and aquatic chronic toxicity (with Aquatic Acute 1 – H400, Aquatic Chronic 1 – H410, M-factor 1 (CLP) and N; R50-53 with corresponding concentration limits (DSD)). This original proposal was commented on during public consultation. Disagreement with the proposed precautionary classification based on the absence of reliable data was expressed by some parties and classification was considered inappropriate. Others supported the precautionary classification or expressed sympathy with the need to classify based on available data but recommended that supporting data be added to strengthen the proposal.

In response to these comments, the dossier submitter amended the classification proposal to a (downgraded) classification for aquatic chronic toxicity (with Aquatic Chronic 2 – H411 (CLP) and N; R51-53 (DSD)).

Limited data are available on the degradability of 2,5-DCBME. At pH 4 and pH 7, 2,5-DCBME hydrolysis is slow with DT_{50} values of 686 and 389 hours, respectively, but at pH 9 the hydrolysis is faster with a DT_{50} of 8.8 hours. The expected primary hydrolysis products are 2,5-dichlorobenzoic acid and methanol. The presence of these products was not monitored in the hydrolysis study. Methyl 2,5-dichlorobenzoate undergoes slow photolysis in water with calculated DT_{50} values of 83-547 days at latitude 50 °N. No information is available on the biodegradability of 2,5-DCBME. No information on the degradation or toxicity of the breakdown products is presented. Methyl 2,5-dichlorobenzoate must be considered as not rapidly degradable (CLP) and not readily degradable (DSD) for the purpose of classification and labelling as it does not degrade biotically or abiotically in the aquatic environment to a level > 70% within a 28-day period and the available data do not demonstrate that the breakdown products are classifiable.

Methyl 2,5-dichlorobenzoate has a log Kow of 3.46. No measured BCF values are available.

The acute aquatic toxicity of 2,5-DCBME has been assessed in fish, crustaceans and algae. The $LE(C)_{50}$ obtained in fish, crustaceans (Daphnia) and algae were 30.66 mg/l, 7.5 mg/l and 12.5 mg/l, respectively, based on nominal concentrations. Chronic toxicity values are only available for algae with a NOEC of 1.4 mg/l, based on a nominal concentration. However, due to the rapid decline of test substance concentrations in the medium, attributed to hydrolysis and/or volatilization, the nominal concentrations do not reflect the actual exposure concentrations. The test substance concentrations were only measured at the beginning of the study and at termination; at test termination, no 2,5-DCBME could be detected in any of the studies. The actual toxicity of 2,5-DCBME could therefore have been underestimated.

Given the nominal 48 h EC_{50} of 7.5 mg/l for Daphnia, and the fact that 2,5-DCBME must be considered as not rapidly/readily degradable, the criteria for classification for aquatic chronic toxicity, category 2 (for $L(E)C_{50}$ values between 1 and 10 mg/l) are met (Aquatic Chronic 2 – H411 (CLP); N; R51-53 (DSD). This should be considered as a minimum classification. As the currently available experimental data for 2,5-DCBME do not enable another classification to be considered, RAC did some QSAR predictions and analysed some structurally similar substances, in order to establish whether another classification is more appropriate for 2,5-DCBME. Given the limitations for RAC elaborations to go beyond the information provided in the dossier and during public consultation, it should be noted that this additional work by RAC was clearly more limited than the thorough and structured QSAR and read across analysis that would be expected from a dossier submitter for effective decision support.

The QSAR program ECOSAR (v1.00) was used to predict the aquatic toxicity of 2,5-DCBME, using the model for esters (valid for a.o. benzoates where the log Kow is below the range 5-8 and (for solids) the $L(E)C_{50}$/NOECD does not exceed the water solubility). The measured log Kow value (3.46), melting point (34.6°C) and water solubility (87 mg/l) were used in the calculations. The following results were obtained:

Fish 96-h LC_{50} = 4.1 mg/l
Daphnid 48-h LC_{50} = 6.9 mg/l
Mysid shrimp 96-h LC_{50} = 2.7 mg/l
Green algae 96-h EC_{50} = 2.5 mg/l

In an analysis of substances that are structurally similar to 2,5-DCBME (ECHA, 2012), it was found that substances similar to 2,5-DCBME often have a harmonised classification for environmental hazards. However, some are not classified, indicating that aquatic toxicity may be very sensitive to the molecular structure. It would therefore generally be preferable to rely on data on the specific substance rather than attempting a read-across. Nevertheless, a structure-activity analysis was attempted, based on the assumption that the substitution pattern of the phenyl-ring influences the overall reactivity, the reaction rate being faster the more electron-withdrawing groups are present on the aromatic ring. The phenyl-ring in 2,5-DCBME is connected to two chlorine atoms, which are electron-withdrawing groups, and to one methylester-group, which is also electron-withdrawing when connected as $–C(=O)OCH_3$.

Three substances were used for read across. The first substance has a phenyl-ring with one halogen and a methylester-group (connected as $–OC(=O)CH_3$) attached. When connected in this way, the ester-group is electron-donating. This substance is classified as Aquatic Chronic 2. Compared to this substance, the reactivity of 2,5-DCBME is expected to be higher, because 2,5-DCBME has more (and stronger) electron-withdrawing groups and no electron-donating group. With an expected higher reactivity, leading to a higher toxicity, 2,5-DCBME should thus also be classified for aquatic toxicity.

The second substance also has a phenyl-ring connected to a methylester-group and to one halogen, but in this case the methylester is connected as in 2,5-DCBME. Additionally,

this substance has an electron-donating amine group connected to the phenyl-ring. It is classified as Aquatic Chronic 3. Compared to this substance, the reactivity of 2,5-DCBME is again expected to be higher, because 2,5-DCBME has more (and stronger) electron-withdrawing groups and no electron-donating group. Consequently, 2,5-DCBME should also be classified.

In a third substance (50% pure) used for read-across, which is classified as Aquatic Chronic 3, the phenyl-ring is connected to two chlorine atoms and to both an acid- and a methoxy-group. The latter group is electron-donating, whereas the acid-group is electron-withdrawing. Given that 2,5-DCBME has no electron-donating group, its reactivity is expected to be higher and thus it should also be classified.

All in all, the QSAR predictions and the analysis of structurally similar substances are considered to substantiate the need for classification for aquatic toxicity, but they are not considered sufficient to judge whether a more stringent classification than the minimum classification is necessary.

Based on all available information, RAC supports the conclusion of the dossier submitter that 2,5-DCBME should be classified for aquatic chronic toxicity with **Aquatic Chronic 2 – H411** (CLP) and **N; R51-53** (DSD, no specific concentration limits necessary). The classification may need to be reviewed if any valid aquatic toxicity data become available.

Reference:

WHO (1997) Benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and the benzoate salts. Chapter 3.6.1 in *Evaluation of certain food additives and contaminants* (Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives), WHO Technical Report Series, No. 868, 1997.

EFSA (2008) Conclusion on the peer review of 2,5-dichlorobenzoic acid methylester, EFSA Scientific Report, 180, 1-50, 2008.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and RAC (excl. confidential information)