Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

4-cyclododecyl-2,6-dimethylmorpholine; Dodemorph (ISO)

EC Number: 216-474-9
CAS Number: 1593-77-7

CLH-O-0000002170-89-02/F

Adopted

13 September 2013

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13 September 2013

CLH-O-0000002170-89-02/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 Regulation (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:

Chemicals name: **4-cyclododecyl-2,6-dimethylmorpholine; Dodemorph (ISO)**

EC Number: **216-474-9**

CAS Number: **1593-77-7**

The proposal was submitted by **the Netherlands** and received by RAC on **14 August 2012.**

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).

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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 **18 December 2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **10 February 2013**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Elodie Pasquier**

Co-rapporteur, appointed by RAC: **José Luis Tadeo**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2. The RAC opinion on the proposed harmonised classification and labelling was adopted on **13 September 2013** by **consensus.**

OPINION OF THE RAC

RAC adopted the opinion that dodemorph (ISO) should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Aquatic Chronic 2	H319 H335 H315 H411	GHS07 GHS09 Wng	H319 H335 H315 H411		
Dossier submitters proposal	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	**Add** Repr. 2 Aquatic Acute 1 **Modify** Aquatic Chronic 1 **Remove** Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	**Add** H361d H400 **Modify** H410 **Remove** H319 H335 H315	**Retain** GHS09 **Add** GHS08 **Modify** Dgr **Remove** GHS07	**Add** H361d **Modify** H410 **Remove** H319 H335 H315		**Add** M=1 M=1
RAC opinion	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	**Add** Repr. 2 STOT RE 2 Skin Corr. 1C Skin Sens. 1A Aquatic Acute 1 **Modify** Aquatic Chronic 1 **Remove** Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	**Add** H361d H373 (liver) H314 H317 H400 **Modify** H410 **Remove** H319 H335 H315	**Retain** GHS07 GHS09 **Add** GHS05 GHS08 **Modify** Dgr	**Add** H361d H373 (liver) H314 H317 **Modify** H410 **Remove** H319 H335 H315	**Add** EUH071	**Add** M=1 M=1

Resulting Annex VI entry if agreed by COM	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	Repr. 2 STOT RE 2 Skin Corr. 1C Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	H361d H373 (liver) H314 H317 H400 H410	GHS05 GHS07 GHS08 GHS09 Dgr	H361d H373 (liver) H314 H317 H410	EUH071	 M=1 M=1

Classification and labelling in accordance with the criteria of Directive 67/548/EEC (DSD)

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits
Current Annex VI entry	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	Xi; R36/37/38 N; R51-53	Xi; N R: 36/37/38-51/53 S: (2-)26-61	
Dossier submitters proposal	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	**Add** Repr. Cat.3; R63 **Modify** N; R50-53 **Remove** Xi; R36/37/38	**Add** Repr. Cat.3; R63 **Modify** N; R50-53 **Remove** Xi; R36/37/38	**Add** N; R50-53: C ≥ 25 % N; R51-53: 2,5 % ≤ C < 25 % R52-53: 0,25 % ≤ C < 2,5 %
RAC opinion	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	**Add** Repr. Cat. 3; R63 C; R34 R43 **Modify** N; R50-53 **Remove** Xi; R36/37/38	**Add** Repr. Cat.3; R63 C; R34 R43 **Modify** N; R50-53 **Remove** Xi; R36/37/38	**Add** C; R34: C ≥ 10 % Xi; R36/37/38: 5 % ≤ C < 10 % N; R50-53: C ≥ 25 % N; R51-53: 2,5% ≤ C < 25 % R52-53: 0,25 % ≤ C < 2,5 %
Resulting Annex VI entry if agreed by COM	613-057-00-7	dodemorph (ISO); 4-cyclododecyl-2,6-dimethylmorpholine	216-474-9	1593-77-7	Repr. Cat. 3; R63 C; R34 R43 N; R50-53	Xn; C; N R:34-43-63-50/53 S: (1/2-)26-28-36/37/39-45-60-61	C; R34: C ≥ 10 % Xi; R36/37/38: 5 % ≤ C < 10 % N; R50-53: C ≥ 25 % N; R51-53: 2,5% ≤ C < 25% R52-53: 0,25 % ≤ C < 2,5 %

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

Hazards addressed in the RAC's opinion

Dodemorph has a harmonised classification and RAC was requested to evaluate the proposals for changes to the harmonised classification. Parallel full evaluation by the RAC of **dodemorph acetate** which is not currently harmonised, raised an additional concern based on repeated dose toxicity studies, which suggested classification for specific target organ toxicity (STOT RE) that also applies to dodemorph. In addition, a comment was made during public consultation on skin sensitisation and this endpoint was additionally addressed by RAC.

RAC's evaluation has therefore focused on proposals for changes to the harmonised classification (irritation/corrosion including respiratory irritation, reproductive toxicity and environment), skin sensitisation and specific target organ toxicity following repeated doses.

Other endpoints were not evaluated in the current opinion.

Use of dodemorph acetate data to evaluate health hazards for dodemorph

No data are available on dodemorph and all toxicological studies presented in the CLH report were performed with dodemorph acetate that is the substance actually manufactured and put on the market (see fig; 1 and 2 for the respective structural formula).

Fig. 1 *– Structural formula of dodemorph*

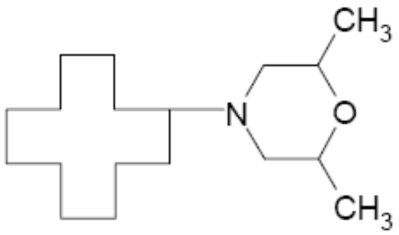
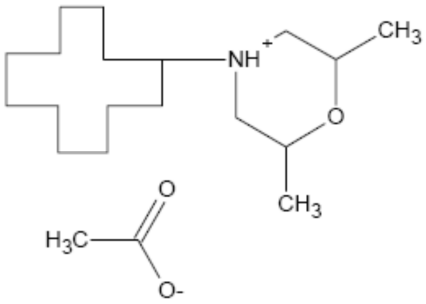


Fig. 2 *– Structural formula of dodemorph acetate*



Dodemorph acetate is a salt which in aqueous environments consists of dodemorph-$H^{(+)}$ (quaternary ammonium ion) and $Acetate^{(-)}$ at pH < 6.5 or dodemorph and $Acetate^{(-)}$ at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist.

RAC therefore agrees that the systemic effects of dodemorph acetate can all be attributed to the dodemorph moiety and are therefore relevant for dodemorph classification.

The Dossier Submitter did not support the use of data from dodemorph acetate for the local effects of dodemorph and proposed to remove the existing classification based on lack of appropriate data.

Regarding local effects of dodemorph acetate (irritation/corrosion and skin sensitisation), it is hypothesised by the Dossier Submitter that they were caused by the formation of a quaternary ammonium ion (dodemorph-H+), which is present in solutions with dodemorph acetate at pH < 10,5. The formation of a quaternary ammonium ion from dodemorph is limited due to an increased pH and a decreased solubility.

However, it is noted that hydrolysis studies of dodemorph acetate in buffered aqueous solutions at pH 4, 5, 7 and 9 (see environmental hazard assessment) concluded that the dodemorph moiety is hydrolytically stable. Other degradation products were either absent or represent less than 10%

(unknown metabolite). A photodegradation study at pH 5, 7 or 9 investigated the metabolites in greater detail but did not report a quaternary ammonium. An unidentified metabolite was reported in low quantity: at pH 5, it amounts to 0.2% at the start of the study and 0.5% after 119 h; at pH 7: 0.6% at the start and 1.7% at 24h; at pH 9: 0.3% at the start and 1.6% at 25h.

From the available data, it is therefore concluded that the formation of a quaternary ammonium from dodemorph acetate in amounts sufficient to induce irritant/corrosive effects is not confirmed. If a quaternary ammonium is not involved in the irritant/corrosive effects induced by dodemorph acetate, it cannot be concluded that dodemorph will not produce similar local effects on the basis of its absence.

As an uncharged molecule dodemorph is likely to be significantly less water soluble than the salt dodemorph acetate. However, once solubilised both dodemorph and dodemorph acetate are present as an equilibrium between dodemorph-H+ and dodemorph, dodemorph-H+ being predominant at acidic and neutral pH and dodemorph at basic pH (pKa of 8.5).

The local effects of dodemorph are therefore expected to be similar to the local effects of dodemorph acetate, considering that water is present in the eye, in the respiratory tract and on the skin due to sweat.

Therefore, RAC considers (contrary to the Dossier Submitter's proposal) that local effects of dodemorph acetate are relevant for the classification of dodemorph.

HUMAN HEALTH HAZARD ASSESSMENT

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

Summary of the Dossier Submitter's proposal

Dodemorph is currently classified STOT SE 3 – H335 for respiratory irritation.
Relevant data available to assess respiratory irritation of dodemorph relates to dodemorph acetate and its corrosive potential (there being no experimental study available for respiratory irritation).
However, as discussed above under "RAC general comment", Dossier Submitter does not support the use of data from dodemorph acetate for the local effects of dodemorph and proposes to remove the existing classification based on lack of appropriate data.

Comments received during public consultation

One MSCA supported the proposal of removal of the existing classification while two MSCA commented that the classification should be retained.

Assessment and comparison with the classification criteria

Based on its corrosive effects (no experimental study available for respiratory irritation), dodemorph acetate is recommended by RAC to be classified EUH071 under CLP and Xi; R37 at concentrations ranging from 5% up to 10% under DSD. The potential of dodemorph acetate to be a respiratory irritant is covered by the proposal to add EUH071: "Corrosive to the respiratory tract"

As discussed above under "RAC general comment", RAC considers that local effects of dodemorph acetate are relevant for classification of dodemorph. Evidence for the corrosivity of dodemorph is detailed in the section "RAC evaluation of skin corrosion/irritation".

In conclusion, RAC recommends to assign the supplemental hazard code EUH071 to dodemorph under CLP and to apply Xi; R37 at concentrations ranging from 5% up to 10% under DSD.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Dodemorph is currently classified Skin Irrit. 2 - H315 for skin irritation.
Relevant data available to assess skin irritation/corrosion of dodemorph relates to dodemorph acetate. As discussed above in the section "RAC general comment", the Dossier Submitter does not support the use of this data for dodemorph and proposes to remove the existing classification based on lack of appropriate data.

Comments received during public consultation

One MSCA supported the proposal of removal of the existing classification while two MSCA commented that the classification should be retained.

Assessment and comparison with the classification criteria

Based on experimental data, dodemorph acetate is recommended by RAC to be classified Skin Corr. 1C – H314 under CLP.

As discussed above under "RAC general comment", RAC considers that local effects of dodemorph acetate are relevant for classification of dodemorph.
Besides, dodemorph is a tertiary amine and other tertiary amines such as triethylamine and tripropylamine are classified as corrosive. More specifically, dodemorph is a morpholine derivative. Other tertiary amine morpholine derivatives such as Tridemorph (CAS 24602-86-6) and Fenpropimorph (CAS 67564-91-4) are classified as Skin Irrit 2 (harmonized classification). Although not all tertiary amines are considered as corrosive, this tends to support the conclusion that the irritant/corrosive properties of these compounds are likely to be linked to the presence of a tertiary amine moiety.
In addition, it is not expected that the corrosive effect of dodemorph acetate is attributed to the acetate moiety.

In conclusion, RAC recommends that dodemorph be classified as Skin Corr. 1C - H314 under CLP and C; R34 under DSD.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier Submitter's proposal

Dodemorph is currently classified Eye Irrit. 2 - H319 for eye irritation.
Relevant data available to assess eye irritation/corrosion of dodemorph relates to dodemorph acetate. As discussed above in the section "RAC general comment", the Dossier Submitter does not support the use of this data for dodemorph and proposes to remove the existing classification based on lack of appropriate data.

Comments received during public consultation

One MSCA supported the proposal of removal of the existing classification while two MSCA commented to maintain the classification.

Assessment and comparison with the classification criteria

Dodemorph acetate is a severe eye irritant based on experimental data. However, a classification for this endpoint is not required given that it is to be classified as corrosive to skin.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Dodemorph is currently not classified for skin sensitisation.
Relevant data available to assess skin sensitisation of dodemorph relates to dodemorph acetate. Dodemorph acetate is a skin sensitiser with a high potency based on experimental data. As

discussed above in the section "RAC general comment", the DS does not support the use of this data for dodemorph.

Comments received during public consultation

One MSCA supported consideration of the local effects of dodemorph for dodemorph acetate and suggested a discussion on the application of the skin sentisation classification of dodemorph acetate to dodemorph.

Assessment and comparison with the classification criteria

Based on experimental data, dodemorph acetate is recommended by RAC to be classified Skin Sens. 1A – H317 under CLP.
As discussed above under "RAC general comment", RAC considers that local effects of dodemorph acetate are relevant for classification of dodemorph.
In conclusion, RAC recommends to classify dodemorph as Skin Sens. 1A (H317) under CLP and Xi; R43 under DSD.

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

Summary of the Dossier Submitter's proposal

Dodemorph is currently not classified for repeated dose toxicity. Relevant data available to assess repeated dose toxicity of dodemorph relates to dodemorph acetate.

Sub-acute and semi-chronic oral studies in the rat and the dog were available. In these studies the main targets for dodemorph acetate were body weight (gain) and the liver.

Reductions in body weight (gain), often accompanied to a lesser extent by a reduction in food consumption, was observed in 3 out of 5 oral studies. The liver appears to be the main target organ. An increase in relative liver weight was observed in 4 out of 5 oral studies. In 3 semi-chronic studies, one in the rat and two in the dog, histological changes indicative of liver damage were found. In the semi-chronic dog studies the increased blood levels of alanine aminotransferase (ALAT) and alkaline phosphatase (AP) indicate that dodemorph acetate induced hepatocellular damage and were consistent with cholestasis. The 1-year study in the dog provided the lowest NOAEL (10 mg/kg bw/day), based on histological changes in the liver (bile duct hyperplasia, peribiliary fibrosis) observed at 25 mg/kg bw/day and higher. In addition, gastric erosion was observed at doses of 25 mg/kg bw/day and higher, which can probably be attributed to the corrosive nature of dodemorph acetate.

The Dossier Submitter concluded that dodemorph acetate did not fulfil the criteria for oral repeated dose toxicity classification, especially as the LOAEL in the 90-day rat study was clearly above the (classification) cut off value. Further to this, in a comment provided in writing during the period of discussion by RAC, the Dossier Submitter argued that the liver toxicity seen in dogs provided only a "borderline case" for classification. The marked degenerative effect in the 90-day study was observed in only 1/6 dogs at a dose relevant for classification and a comparable effect was not seen in the longer study of 1-year duration (except in 1 female dog killed for ethical reasons at 62.5 mg/kg). Further, although bile duct effects were seen at relevant doses, the Dossier Submitter noted that they were of "slight to mild severity" and therefore concluded that they were not sufficiently severe to support classification.

The Dossier Submitter also commented that the local gastric irritation did not warrant classification with STOT RE. This was an effect mainly determined by concentration and not by dose, that was only observed after exposure via capsule but not after exposure via diet. The relevance of this route (capsule) for this type of effect was considered limited.

Dermal application for 21 days of dodemorph acetate at doses up to and including 60 mg/kg bw/day did not result in systemic effects. At a dermal dose of 60 mg/kg bw/day local effects (erythema, oedema, scab formation) were observed. The NOAEL for local dermal effects was 12 mg/kg bw/day.

For dermal repeated dose toxicity, the LOAEL is lower than the cut-off value for classification. However, all observed effects are due to the corrosive properties of dodemorph acetate.

Comments received during public consultation

There were no comments relating specifically to this endpoint.

Assessment and comparison with the classification criteria

The liver and the gastro-intestinal tract are the key target organs following repeated exposure to dodemorph acetate. The relevant findings from the available repeated dose toxicity studies are summarised in the following table.

Main results from the repeated dose toxicity studies

Study design	**Doses** **(doses relevant for classification in bold and underlined)**	**Severe effects at doses relevant for classification**	**Other significant adverse effects at doses relevant for classification**
Studies involving oral exposure			
Rat, 28 days, diet	0, **<u>50</u>** & **<u>100</u>** mg/kg bw/day (approx)	None	None
Rat, 42+ days, diet one-generation range finding study, diet exposure from at least 42 days before mating up to day 21 after birth of pups.	0, **<u>70/63</u>**, 140/123 & 271/238 mg/kg bw/day for males/females)	None	None
Rat, 90 days, diet	0, **<u>20</u>**, **<u>40</u>** & **80** mg/kg bw/day (approx)	None	None
Rat, 90 days, diet (OECD 408)	0, **<u>20/23</u>**, **79/94**, & 229/259 mg/kg bw/day for males/females (approx)	None	None
Rat, 70+ days, diet two-generation study; OECD 416	0, **<u>21</u>**, **<u>64</u>** & 194 mg/kg bw/day	None	None
Rat, 2-year, diet OECD 453	0, **<u>16/21</u>**, 55/73 & 166/222 mg/kg bw/day for males/females (approx)	None	None
Mouse, 18-month, diet OECD 451	0, 45/55, 152/184 & 455/545 mg/kg bw/day for males/females (approx)	None	None
Dog, 28 days gavage	0, **<u>40</u>**, **<u>80</u>** & 160 mg/kg bw/day	None	Vomiting & salivation at 80 mg/kg bw/day
Dog, 90 days diet	0, **<u>32/33</u>**, **<u>79/79</u>** & 187/194 mg/kg bw/day for males/females (approx)	At 79 mg/kg bw/day: marked degenerative changes in the liver (1/6 dogs).	At 32/33 mg/kg bw/day: moderate fatty degeneration in the liver (1/6 dogs). At 79 mg/kg bw/day: clinical chemistry

			indicative of liver damage (increased ALAT & AP), increased absolute and relative liver weights, pale liver, moderate degenerative changes (5/6 dogs), moderate fatty degeneration (2/6 dogs).
Dog, 1 year capsule OECD 452	0, **<u>10</u>**, **<u>25</u>** & 62.5 mg/kg bw/day	25 mg/kg bw/day: slight (3/8 dogs) or mild (1/8 dogs) bile duct hyperplasia, associated with slight peribiliary fibrosis (4/8 dogs). Local effects: microscopic and macroscopic gastric lesions (including gastric erosion) in some dogs, associated with corrosive nature of test substance.	25 mg/kg bw/day: vomiting and salivation.
<u>Studies involving dermal exposure</u>			
Rabbit, 21 days	0, **2.4**, **12** and **60** mg/kg bw/day (aq. Solutions)	No systemic effects Local effects at 60 mg/kg bw/day (2% solution): progressive development of erythema, oedema and scab formation	None

The findings in rats and mice do not support classification. However, the lesions observed in the liver in dogs following 90 days and/or 1 year exposure to dodemorph acetate demonstrate a concern and, although the comments of the Dossier Submitter are noted, these findings do provide evidence for classification of dodemorph.

Generally, severe or "significant" adverse effects (i.e., "changes that clearly indicate functional disturbance" as defined in section 3.9.2.2 of the CLP guidance) in 90-day repeat dose studies trigger classification with STOT RE if they are seen at doses of 100 mg/kg bw/day or lower. The observation of treatment-related, marked degenerative changes in one of six dogs given 79 mg/kg bw/day dodemorph acetate per day for 90 days is compatible with the criteria for STOT RE 2. The observation of similar, but more moderate findings in all the remaining dogs at this dose and some limited evidence of liver toxicity in one dog at the lower dose of about 30 mg/kg bw/day further support the case for STOT RE 2.
Similarly, the bile duct hyperplasia, associated with peribiliary fibrosis (a non-reversible toxicity), seen in dogs at 25 mg/kg bw/day in the 1-year dog study, is viewed as supporting evidence.

Although there were no comparable findings in the repeat dose studies with rats or mice, RAC concludes that this level of liver toxicity seen in dogs is sufficient to justify classification of dodemorph with STOT RE 2. There is no evidence to suggest that the findings have no or limited relevance to humans and, in addition, the effective doses are sufficiently low to meet the criteria for classification.

Repeated exposure to dodemorph acetate in capsule form produced macroscopic and microscopic lesions in the gastro-intestinal tract in some dogs at 25 mg/kg bw/day. As explained by the Dossier Submitter, these lesions were a consequence of the concentrated capsular form in which the corrosive test substance was administered in this study, the dose not being the key determinant. Given that dodemorph acetate and dodemorph is to be classified as a corrosive substance, RAC agreed with the Dossier Submitter that no further classification was supported by these findings.

As discussed under "RAC general comment", systemic effects of dodemorph acetate are attributed to the dodemorph moiety and effects observed in the liver further repeated exposure to dodemorph acetate are therefore relevant for classification of dodemorph.

As for dodemorph acetate, RAC concludes that classification of dodemorph with STOT RE 2: H373 (May cause damage to the liver through prolonged or repeated oral exposure) is warranted under CLP.

Due to lower thresholds than in CLP for classification for repeated dose toxicity (below 50 mg/kg bw/day in a 90-day study and 12.5 mg/kg bw/day for a one-year study), no classification is justified under DSD.

Repeated topical dosing of rabbits with dodemorph acetate for 21-days produced no systemic effects. The local lesions observed were consistent with the potential corrosivity of the neat substance to the skin. As this hazard is already covered by the classification Skin Corr. 1C, no further classification is needed.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Dodemorph is currently not classified reproductive toxicity.
Relevant data available to assess reproductive toxicity of dodemorph relates to dodemorph acetate.

Fertility and reproductive function

A rat 1-generation range finding study and a rat 2-generation study (OECD 416) are available. In the range finder, there was a dose-related decrease in mean litter size (15.3, 15.0, 13.6, 11.7 at 0/0, 70/63, 140/123 and 271/238 mg/kg bw/day, in males/females, respectively). At the top dose, in F1 pups there was also a reduced viability index, a decreased body weight on day 1 and decreased body weight gain on days 4-21. The parental animals themselves exhibited dose-dependent reductions in food consumption and body weight gain, which were statistically significant at the top dose. There was no effect on mating or fertility. The most relevant findings are summarised in the Table below.

Main results from 1-generation reproductive toxicity study (range-finding) in the rat

	Dose (ppm)	**0**	**0**	**600**	**600**	**1200**	**1200**	**2400**	**2400**
	Sex	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
F0 animals	Body weight gain as % change from control -premating -gestation	N/A	N/A	 -4	 -9 +1	 -3	 -11 -11	 -18*	 -21* -27*
	Food consumption	N/A	N/A						

	Dose (ppm)	0	0	600	600	1200	1200	2400	2400
	Sex	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
	as % change from control -premating during gestation during lactation			-1	-4 -1 -2	-1	-6 -7 -9	-8*	-12* -14* -36*
F1 pups	Litter size	15.3		15.0		13.6		11.7*	
	viability index as % survivors, day 0-4	95		96		95		61*	
	Body weight day 1	6.1	5.8	6.1	5.9	6.2	6.0	5.7	5.1*
	Grams body weight gain day 4-21 (% of control)	41.9	39.6	39.7 (-5)	38.7 (-2)	38.3 (-9)	36.7 (-7)	30.0 (-28)	29.6 (-27)

* significantly different; N/A: not applicable

In the 2-generation study, there was a reduction in food consumption and body weight gain of parental (F0 and F1) animals at the highest dose (approx. 194 mg/kg bw/day). Additionally, there was an increased incidence in minimal hypertrophy of periacinar hepatocytes (F0 and F1 females), a reduction in absolute kidney weights (males and females) and a reduced absolute epididymides weight. However, these findings were considered to be related to the decreased body weight, and not directly related to dodemorph acetate toxicity.

Compared to the gestation duration in control animals (22 days), slight but statistically significant reductions in gestation duration were observed for the F1a (21.6 days) and F1b (21.4 days) litters in the top dose group and for the F1b litters (21.6 days) of the mid-dose group. These data were outside the historical control range (21.7-22.5 days). No effects were observed on gestation duration for the F2 generation. It should be noted that day 0 of gestation was defined by the day on which sperm was detected after a male and female were mated for a period of about 16 hours. The birth of the litter was generally evaluated in the mornings in connection with the clinical observation. According to the CLH report, the method of establishing both the start of gestation and the birth of the pups lacked accuracy. In view of the small size of the effect, the lack of an effect in the gestation duration of the F2 generation and the lack of accuracy in establishing the gestation duration, these effects are considered not toxicologically relevant.

In pups, at the high dose, there was a reduced viability index and a reduced body weight at day 1 (approximately -10% in the F1a and F1b generations and -6/7% in F2). There was a reduced body weight gain during lactation and a decreased incidence of pups with normal physical development landmarks (pinna [earflap] unfolding, auditory canal opening and eye opening) at the high dose. There was also significantly reduced body weight gain from day 4-21 (approximately -7% in both F1a and F2) and significantly decreased pinna unfolding also in the mid dose groups. Main findings are summarised in the following table.

Main results from 2-generation reproductive toxicity in the rat

	Dose (ppm)	0	0	200	200	600	600	1800	1800
	Sex	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
F0 parents	Body weight gain as % change from control -premating (F1a) -gestation (F1a)	N/A	N/A	-1	-2 +4	-1	-2 +4	-13*	-18* -9
	Food consumption as % change from control -premating (F1a) -gestation (F1a)	N/A	N/A	0	0 +4 -4	+1	0 +4 -4	-6	-10* -7* -14*

	Dose (ppm)	0	0	200	200	600	600	1800	1800
	Sex	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
	-lactation (F1a)								
F1a,b pups	Viability index F1a F1b	98 95		97 94		98 95		87* 92	
	lactation index F1a F1b	96 99		99 98		99 99		100 96*	
	Physical development [A] F1a Pinna unfolding auditory canal opening eye opening F1b Pinna unfolding auditory canal opening eye opening	98.2 100 95.1 95.5 96.7 93.2		93.1 96.9 99.5 82.1 94.4 90.6		89.6 95.8 91.8 79.7* 98.4 87.4		68.4* 79.3* 71.4* 53.0* 73.6* 62.5*	
	Body weight (g) day 1 F1a F1b	6.6 6.5	6.2 6.1	6.6 6.5	6.3 6.1	6.5 6.3	6.2 6.1	5.9* 5.8*	5.7* 5.5*
	Body weight gain (g) F1a day 1-4 day 4-21 F1b day 1-4 day 4-21	3.1 45.7 2.7 43.3	2.9 43.1 2.6 41.3	2.8 44.2 2.7 41.9	2.9 42.2 2.5 39.4	2.6 42.5* 2.3 41.5	2.5 40.2* 2.2 39.7	2.1* 34.4* 2.0* 34.5*	2.1* 33.3* 1.8* 32.8*
F1 parents	Body weight gain as % change from control -premating -gestation	N/A	N/A	0	+1 0	-2	-4 -7	-7*	-6* -19*
	Food consumption as % change from control -premating -gestation -lactation	N/A	N/A	-1	0 +2 -3	0	-1 +2 -3	-6*	-7* -7* -25*
F2 pups	viability index	96		94		98		79*	
	Body weight day 1	6.5	6.1	6.4	6.1	6.8	6.5	6.1*	5.7*
	Body weight gain day 1-4 day 4-21	2.9 43.7	2.8 41.9	2.9 42.9	2.7 40.8	2.8 40.6*	2.7 38.3*	1.7* 32.4*	1.7* 30.8*
	Physical development [A] Pinna unfolding auditory canal opening eye opening	92.7 99.5 93.8		92.3 100 97.4		96.9 97.6 97.2		73.3* 73.5* 78.7*	

* significantly different; dr = dose related; N/A: not applicable

[A] Developmental stage, % of pups reaching criteria. Pinna unfolding at day 4, auditory canal opening at day 13, eye opening on day 15.

No treatment-related effects of dodemorph acetate on reproductive function were observed in either of these studies.

Developmental toxicity

In a rat developmental study with dodemorph acetate doses of 30-300 mg /kg bw/day, no developmental effects were observed at the highest dose that did not induce maternal toxicity (30 mg/kg bw/day). However, at the top dose, statistically significant increased litter incidences of misshapen sternebrae, unossified sternebrae and incomplete ossification of the lumbar arch were found. These incidences were at the upper end or above the historical control range. At this dose, maternal toxicity was evident from impairments in body weight and body weight gain, decreased food consumption, increased liver weight (>10%), a marked increase in triglycerides and slight deviations in serum electrolytes and increased platelets. Main findings are summarised in the following table.

Main results from the developmental toxicity study in rats

	Dose (mg/kg bw per day)	**0**	**30**	**100**	**300**	**HCD[2]: mean (range)**
Maternal findings	Corrected body weight gain in grams (% of control) [1]	33.7	31.6 (-6)	26.0 (-23)	20.4* (-31)	-
	Food consumption GD 6-13 as % of control	N/A	91 %	79%	53%*	-
	Clinical chemistry - triglycerides (mmol/L)	5.01	6.15	7.37	11.06*	-
	Relative liver weight as % change from control	N/A	0.5	1	17*	-
Foetal findings	Skeletal variations (litter incidences in %)					
	- misshapen sternebra	64	82	76	90*	67 (25-92)
	- unossified sternebra	24	23	19	52*	30 (17-46)
	- incomplete ossification of lumbar arch	0	5	0	21*	1 (0-4)

* statistically significant
\- no data; N/A: not applicable
[1] Corrected body weight gain = terminal body weight minus uterine weight minus day 6 body weight.
[2] Historic control data were included in the study report and consisted of 9 gavage studies and 1 inhalation study in Wistar rats from the same supplier, performed in the period of January 2000 up to June 2001.

In a rabbit developmental study, no maternal toxicity was observed. The NOAEL for maternal toxicity was 120 mg/kg bw/day (the highest dose tested). In the rabbit foetuses, a slight increase in incidence of malformations (cleft palate in 1 foetus and open eye in 4 foetuses, only in one litter) was observed at the highest dose level, and the percentage of animals with irregularly shaped sternebrae was increased. Although in this study the open eye was observed only in one litter, open eye was also observed in 7 out 16 foetuses from a single litter in the range-finding study in the rabbit at a higher dose level, indicating the effect is dose-related. In the range-finding study anasarca was also observed in 4 out of 16 foetuses from a single litter. No historical control data were provided. Main findings are summarised below.

Results from a developmental toxicity study in rabbits

Dose (mg/kg bw per day)	**0**	**10**	**40**	**120**
Maternal toxicity	No maternal toxicity			
Post implantation loss, in %	6.2	13.0	5.1	18.4
No. of dams with all resorptions	0	0	0	1
No. of early resorptions[a]	0.2	0.3	0.2	0.7
External malformations **- cleft palate (no. of foetuses)** **- open eye (no. of foetuses)**	 0 0	 0 0	 0 0	 1 4
Skeletal variations/retardations **- sternebra irregular shape (foetuses/litter)**	1.6	5.0	6.0	10.9*

* statistically significant

[a] unit not specified in CLH report (probably mean foetal incidence by litter)

The Dossier Submitter noted that in the repeated dose toxicity studies, only a slight increase in relative liver weight was observed at 80 mg/kg bw/day in a 90 day study in rats, while in a 28 day study in rats, no effects were observed up to 160 mg/kg bw/day.

The Dossier Submitter proposed the classification Repr. 2; H361d (CLP) and Repr. Cat. 3; R63 (equivalent classification under DSD) based on:

- in the 2 generation study, reduced body weight gain of the pups was observed at a dose without maternal toxicity as well as decreased pinna unfolding in 1 generation.
- in a developmental study with rabbits, an increase in early resorptions and post implantation loss, and in four foetuses from one litter, an increase in the incidence of open eye was observed at the top dose tested (no maternal toxicity).

The Dossier Submitter justified their proposal for a Category 2 classification (CLP), rather than Category 1B, by the argument that these findings were generally not seen consistently in all litters or were not of particularly high severity.

Comments received during public consultation

Two MSCA specifically expressed their support for classification Repr 2 (H361d) in addition to two other MSCA supporting the proposed classification for dodemorph in general. No further explanation was provided with these expressions of support.

Assessment and comparison with the classification criteria

Fertility and reproductive function

RAC agrees with the assessment provided by the Dossier Submitter; no classification is justified.

Developmental toxicity

RAC agrees with the Dossier Submitter that the following findings support the proposal to classify dodemorph for developmental toxicity (on the basis of dodemorph acetate data):

- **Reduction of pup body weight gain during lactation and delay in physical development landmarks.**

The effects are observed in F1a, F1b and F2 generations at the high dose that also produces maternal toxicity (14% decrease in food consumption during lactation). At mid-dose, without maternal toxicity, a significant effect on pup body weight development (day 4-21) in F1a and F2 generations and an effect on pinna unfolding in F1b and F2 generations were also observed. These effects are therefore not considered to be secondary to maternal toxicity.
However, these effects are not considered as severe and may be reversible after cessation of exposure and a classification in category 2 is more appropriate than a category 1B on the basis of these findings.

- **Increase in incidence of malformations at the top dose in the rabbit developmental toxicity study**.
Cleft palate (1 foetus from one litter) and open eyes (4 foetuses from one litter) were reported.
No historical control data were provided in the CLH report. Published historical control data (HCD) on the Himalayan rabbit (Viertel, 2003) reports 4 foetuses with cleft palates (0.052%) from 4 different litters (0.35%) and 7 foetuses with open eyes (0.091%) from 7 litters (0.62%). Although these HCD should be used with care as they relate to a different laboratory, it indicates that cleft palate is a rare malformation in the rabbit but a single incidence cannot be attributed with certainty to the treatment.
Open eyes is also a rare malformation. The observation of 4 incidences in one dose group therefore seems very unusual. As a single litter is affected, this finding is nevertheless in line with the spontaneous isolated incidence reported in the literature. However, open eyes were also reported in the range-finding rabbit study in a similar pattern: a relatively high foetal incidence (7 foetuses affected) but originating from a single litter. Due to the repetition of this finding in the two studies, it is therefore considered unlikely to be of spontaneous origin and this malformation is attributed to treatment.
No maternal toxicity was observed in this study and the effect cannot therefore be secondary to maternal toxicity.

Overall, considering the uncertainty raised by the grouping of cases in single litters and the low litter incidence, RAC considers that a category 2 is however more appropriate than a category 1B on the basis of these findings.

The following effects are also reported and provide supportive evidence for classification in category 2.

In the rabbit developmental toxicity study, in the absence of maternal toxicity:

- An increasing incidence of irregular shaped sternebrae with dose (1.6, 5.0, 6.0 and 10.9 foetuses/litter in the control, low, mid and high dose groups, respectively) that reaches statistical significance at the high dose. This abnormality is reported as a variation in the CLH report but provides supportive evidence for classification in category 2.
- An increased incidence in early resorptions and post implantation loss at the top dose. These effects were not statistically significant and the increase in early resorptions was limited. Besides, in the absence of historical control data, interpretation of the significance of these findings is difficult. It is noted that effects on post-implantation loss were also noted in the rabbit range-finding developmental study but in presence of substantial maternal toxicity and an effect secondary to maternal toxicity cannot be excluded. Due to uncertainties in the significance of this observation in the main study and potential link with maternal toxicity in the range-finding study, it provides supportive evidence for classification in category 2.
- In the one-generation and two-generation rat studies: decreased pup body weight at PND 1 and decreased viability at PND 4 in the one-generation and the two-generation rat studies. The effects were seen in the presence of maternal toxicity as evidenced by decreases in food consumption as well as in maternal body weight gain during the whole exposure period and it cannot be excluded that these foetal effects are a secondary non-specific consequence of maternal toxicity.

RAC also notes the following effects induced by dodemorph, although they are not considered sufficient *per se* to justify a classification for development:

skeletal findings in the rat developmental study. Only incidences of unossified sternebrae and incomplete ossification of sternebrae were above the upper limit of historical control data and can be attributed to treatment. Both are generally considered as variations (Solecki 2001) and as changes in the ossification state that do not involve the normal structure of the bone. In the absence of an adverse effect on foetal body weight, they are not considered to be secondary to general foetal developmental delay but they are of insufficient severity to trigger classification. It is however noted that sternebra variations are also reported in the rabbit developmental study as discussed above.
In conclusion, although RAC also noted that adverse findings on development were seen in both rats and rabbits, RAC agrees with the Dossier Submitter that this profile best fitted the criteria for Repr. 2; H361d. The findings could not be dismissed as being of no relevance to humans and, as such, classification was necessary. However, as a clear teratogenic effect had not been observed and the level of foetotoxicity seen was not severe, a Repr. 1B classification seemed inappropriate.

On a similar basis, a classification Repr. Cat. 3; R63 is recommended under DSD.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of the Dossier Submitter's proposal

The Dossier Submitter proposes to harmonise the environmental classification for dodemorph as category Acute 1, H400, with an M-factor 1 and category Chronic 1, H410, with an M-factor 1 according to CLP (according to DSD as N; R50-53 with specific concentration limits as given at the end of this section).

General remark: Most of the studies were performed with dodemorph acetate but given the rapid hydrolysis of dodemorph acetate in aequous solution to dodemorph free base and acetate these studies are also applicable to dodemorph.

Degradation

Degradation was studied in two hydrolysis tests, a photolysis test and an aerobic water/sediment study. A ready biodegradation study was not available.

The Dossier Submitter considers dodemorph as hydrolytically stable. A hydrolysis study with ^{14}C-dodemorph acetate showed its rapid dissociation into dodemorph and acetate whereas dodemorph was found to be hydrolytically stable at pH 5, 7 and 9 at 24-25ºC (DT_{50} > 32 days). In a second study performed with ^{14}C-dodemorph acetate, according to OECD 111, DT_{50} > 5 days was determined at pH 4, 7, and 9 at 22 ºC.

Dodemorph was photolysed rapidly in aqueous solutions; the DT_{50} was equivalent to 3.6 and 1.6 natural sunlight days at pH 7 and 9, respectively.

In a water/sediment study dodemorph dissipated rapidly from a water column but has long half-lives (> 53 days) in the total system. The mineralisation rate was slow (15.4% and 23.2% of the applied radioactivity was completely mineralised after 103 days).

Based on the available data dodemorph was considered not rapidly degradable.

Bioaccumulation

The bioconcentration factor (BCF) of fish (*Oncorhynchus mykiss*) was determined in a flow-through study conducted according to OECD 305. Fish were exposed to dodemorph acetate spiked with radiolabelled dodemorph. BCF values determined for dodemorph in fish varied between 580-750 l/kg. Based on the results the Dossier Submitter concludes that dodemorph is highly bioaccumulative.

Aquatic toxicity

All available studies were performed with dodemorph acetate. Dodemorph acetate dissociates rapidly in aqueous solution into acetate and dodemorph, therefore, dodemorph was the compound determined by HPLC analysis. For the purpose of classification and labelling, the toxicity endpoints expressed as dodemorph acetate were transformed into toxicity endpoints expressed as dodemorph using a conversion factor of 0.82 [281.5 (MW dodemorph) /341.5 (MW dodemorph acetate)] and assuming that the bioavailability for dodemorph was the same as for dodemorph acetate.

Reliable acute and chronic toxicity studies for fish (*Oncorhynchus mykiss*), invertebrates (*Daphnia Magna*) and algae (*Pseudokirchneriella subcapitata)* were reported by the Dossier Submitter. The acute LC_{50} for fish was between 1.23-2.65 mg/l and the chronic NOEC was 0.10 mg/l. The acute EC_{50} for invertebrates was 1.48 mg/l and the chronic NOEC was 0.08 mg/l. The reported acute E_rC_{50} for algae was 0.91 mg/l and the chronic NOE_rC 0.5 mg/l. All studies were performed according to relevant OECD guidelines and the reported $L(E)C_{50}$ and NOEC values were based on mean measured concentrations.

Algae (*Pseudokirchneriella subcapitata*) were the most sensitive species in acute and chronic tests, with an ErC_{50} of 0.91 mg/l and a NOErC of 0.05 mg/l, respectively.

Comments received during public consultation

The environmental hazard classification was supported by three MSCAs with some minor editorial comments.

Furthermore, updated information regarding the solubility and surface tension of dodemorph was submitted during the public consultation. The Dossier Submitter agreed with it, although this new information did not change the proposed classification.

RAC assessment and comparison with criteria

Degradation.

Dodemorph is considered hydrolytically stable at pH 5, 7 and 9 at 24-25ºC with calculated DT_{50} values > 32 days. Dodemorph is photolysed rapidly in an aqueous solution.

In a water/sediment study, dodemorph dissipates rapidly from water but has long half-lives (> 53 days) in the total system. The mineralisation rate is slow (15.4% and 23.2% after 103 days).

Based on the available data, RAC agrees that dodemorph is not readily biodegradable according to DSD and not rapidly degradable according to CLP.

Bioaccumulation

In the current CLP criteria (2^{nd} ATP) bioaccumulation is important only if the surrogate approach is applied for assessing long-term hazards. For dodemorph, adequate chronic toxicity data is available for all trophic levels and, therefore, bioaccumulation data is not used for classification according to CLP. However, under DSD bioaccumulation should be used for assessing long-term adverse effects. BCF values determined for dodemorph in fish varied between 580-750 l/kg and, as they are above the cut-off value of> 100 l/kg, dodemorph is considered as bioaccumulative.

Remark: Dodemorph is a surface active substance (surface tension 55.1 mN/m), for surfactants it may be appropriate to obtain measured Kp and BCF values, as it has been done, therefore this new data submitted during public consultation does not affect the proposed classification.

Aquatic toxicity

Under CLP, classification for acute aquatic hazard is based on the most sensitive species. The reported E_rC_{50} (72-h) for algae (*Pseudokirchneriella subcapita*) equals 0.91 mg/l[i] (mean measured concentrations). This value is below the cut-off value of ≤ 1 mg/l for classification as

acute aquatic hazard. RAC agrees to classify dodemorph as Aquatic Acute 1, H400, with an M-factor of 1, because the $L(E)C_{50}$ is between 0.1 and 1 mg/l.

Regarding the classification for long-term aquatic hazard, algae (*Pseudokirchneriella subcapita*) is also the most sensitive species with a NOErC of 0.05 mg/l (mean measured concentrations). As dodemorph is not rapidly degradable, RAC agrees to classify dodemorph as category Chronic 1, H410, with an M-factor of 1, because the NOEC value is between 0.01 and 0.1 mg/l.

Based on the classification criteria according to DSD, the ErC_{50} (72-h) for the most sensitive species *Pseudokirchneriella subcapitata* of 0.91 mg/l is below the classification criterion of ≤ 1 mg/l. As dodemorph is not readily biodegradable with a log K_{ow} ≥ 3, RAC agrees with the Dossier Submitter's proposal to classify dodemorph as N; R50-53 with the following specific concentration limits:

N; R50-53: C ≥ 25%
N; R51-53: 2,5% ≤ C < 25%
R 52-53: 0,25% ≤ C < 2,5%

ANNEXES:

Annex 1 The Background Document (BD) provides the detailed scientific grounds for the opinion. It is based on the CLH report prepared by the dossier submitter; the evaluation performed by the RAC is contained in the RAC boxes.

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

REFERENCES:

Viertel B, Trieb G (2003). The Himalayan rabbit (*Oryctolagus cuniculus L.*): spontaneous incidences of endpoints from prenatal developmental toxicity studies. Lab Anim. **37**(1):19-36.

Makris S. *et al*. (2009) Terminology of developmental abnormalities in common laboratory mammals (Version 2). *Reprod Toxicol* **86**(4):227–327

Solecki R. *et al*. (2001) Harmonisation of rat fetal skeletal terminology and classification. Report of the Third Workshop on the Terminology in Developmental Toxicology. Berlin, 14–16 September 2000. *Reprod Toxicol* **15:** 713–721

[i] In the CLH report and in the DAR, the exponential growth during the test (24 h and 48 h) has not been submitted, therefore it is not possible to reduce the test period. Test concentrations were checked at the beginning (50% of nominal) and at the end of the test (25% of nominal). Mean measured test concentrations varied between 14% and 36 %. The results are reliable, although, according to the guideline OECD 201, for volatile, unstable or strongly adsorbing test substances, additional samplings for analysis at 24 hour intervals during the exposure period should have been done in order to better define loss of the test substance.