Committee for Risk Assessment

RAC

Annex 1

Background document

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

dodemorph

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

CLH-O-0000002170-89-02/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

13 September 2013

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: Dodemorph

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

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

Index Number: **613-057-00-7**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Dodemorph was included in Annex I of Directive 67/548/EEC and inserted in Annex VI of Regulation (EC) No 1272/2008 (CLP; ATP001). The current classification is probably based on studies with dodemorph acetate. In 2007, a DAR was prepared for inclusion of dodemorph in Annex I to Directive 91/414/EEC; this was amendend in 2008 (Final addendum to DAR on dodemorph, July 2008). This resulted in a different proposal for classification when compared to the classification in Annex VI of CLP. To implement the modifications in Annex VI to Regulation (EC) No 1272/2008, this proposal to modify the harmonised classification and labelling is prepared. Only the endpoints resulting in classification according to the DAR are discussed in this dossier. Although the subject of the evaluation is dodemorph, all toxicological studies have been performed with the variant dodemorph acetate. Dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist. At the meeting of experts (PRAPeR 49, June 2008) it was agreed that the observed effects can all be attributed to the dodemorph moiety of dodemorph acetate. Dodemorph acetate also is the substance actually produced and used.

Table 1: Substance identity

Substance name:	***Dodemorph***
EC number:	***216-474-9***
CAS number:	***1593-77-7***
Annex VI Index number:	***613-057-00-7***
Degree of purity:	***The minimum content of pure dodemorph acetate, the substance used in all toxicological studies, is 950 g/kg in the manufactured material, relative to the dry material. Dodemorph acetate is due to the irritant nature however never produced as pure dry material, but as a solution, avoiding any potential exposure to worker. The specification for the technical concentrate is > 544 g/kg.***
Impurities:	***The substance does not contain any impurities considered relevant for the classification and labelling of the substance.***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation for dodemorph	Eye Irrit. 2; H319 STOT SE 3; H335 Skin Irrit. 2; H315 Aquatic Chronic 2; H411	Xi; R36/37/38 N; R51-53
Current proposal for consideration by RAC for dodemorph	Repro Cat. 2; H361d Aquatic Acute 1; H400 Aquatic Chronic 1; H410 Removal of Eye Irrit. 2; H319 Removal of STOT SE 3; H335 Removal of Skin Irrit. 2; H315 M factor: Acute M-factor of 1 Chronic M-factor of 1	Repro Cat.3, Xn; R63 N; R50 Removal of Xi; R36/37/38 Removal of R51
Resulting harmonised classification for dodemorph (future entry in Annex VI, CLP Regulation)	Repro Cat. 2; H361d Aquatic Acute 1; H400 Aquatic Chronic 1; H410 M factor: Acute M-factor of 1 Chronic M-factor of 1	Repro Cat. 3; Xn; R63 N; R50-53

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Classification for human health and environmental hazards.

The 2nd ATP has implemented the 3rd revised edition of GHS in which classification and assignment of M-factors can also be based on chronic aquatic toxicity. The 2nd ATP will come into force on 1 December 2012. Harmonised classifications using criteria of the 2nd ATP will not be mandatory before 1 December 2012. Based on the criteria of the 2nd ATP, a classification and an M-factor based on the chronic aquatic toxicity is proposed in addition to a classification and an M-factor based on the acute aquatic toxicity.

According to Directive 67/548/EEC and Directive 1999/45/EC as amended by Directive 2006/8, no distinction between acute and chronic SCLs can be made since only acute aquatic toxicity data are allowed for deriving classifications and SCLs. Therefore, only one set of SCL are proposed for classification of dodemorph according to DSD criteria.

Also, sub-classification for the sensitizing properties will be performed.

Table 3: Proposed classification for dodemorph according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	Not classified	none	Not classified	Data lacking
2.2.	Flammable gases	Not classified	none	Not classified	Data lacking
2.3.	Flammable aerosols	Not classified	none	Not classified	Data lacking
2.4.	Oxidising gases	Not classified	none	Not classified	Data lacking
2.5.	Gases under pressure	Not classified	none	Not classified	Data lacking
2.6.	Flammable liquids	Not classified	none	Not classified	Data lacking
2.7.	Flammable solids	Not classified	none	Not classified	Data lacking
2.8.	Self-reactive substances and mixtures	Not classified	none	Not classified	Data lacking
2.9.	Pyrophoric liquids	Not classified	none	Not classified	Data lacking
2.10.	Pyrophoric solids	Not classified	none	Not classified	Data lacking
2.11.	Self-heating substances and mixtures	Not classified	none	Not classified	Data lacking
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	none	Not classified	Data lacking
2.13.	Oxidising liquids	Not classified	none	Not classified	Data lacking
2.14.	Oxidising solids	Not classified	none	Not classified	Data lacking
2.15.	Organic peroxides	Not classified	none	Not classified	Data lacking
2.16.	Substance and mixtures corrosive to metals	Not classified	none	Not classified	Data lacking
3.1.	Acute toxicity - oral	Not classified	none	Not classified	conclusive but not sufficient for classification
	Acute toxicity - dermal	Not classified	none	Not classified	Data lacking
	Acute toxicity - inhalation	Not classified	none	Not classified	Data lacking
3.2.	Skin corrosion / irritation	Not classified	none	Skin irrit 2	Data lacking
3.3.	Serious eye damage / eye irritation	Not classified	none	Eye irrit 2	Data lacking
3.4.	Respiratory sensitisation	Not classified	none	Not classified	Data lacking
3.4.	Skin sensitisation	Not classified	none	Not classified	Data lacking
3.5.	Germ cell mutagenicity	Not classified	none	Not classified	conclusive but not sufficient for classification
3.6.	Carcinogenicity	Not classified	none	Not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Repro Cat. 2	none	Not classified	
3.8.	Specific target organ toxicity –single exposure	Not classified	none	STOT SE 3	Data lacking
3.9.	Specific target organ toxicity – repeated exposure	Not classified	none	Not classified	conclusive but not sufficient for classification
3.10.	Aspiration hazard	Not classified	none	Not classified	conclusive but not sufficient for classification

4.1.	Hazardous to the aquatic environment	Aquatic Acute 1 Aquatic chronic 1	Acute M factor 1 Chronic M factor 1	Aquatic chronic 2	
5.1.	Hazardous to the ozone layer	Not classified	None	Not classified	conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Danger
Hazard statements: H361d; H410
Precautionary statements:

Proposed notes assigned to an entry:

Table 4: Proposed classification for dodemorph according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	Not classified	none	Not classified	Data lacking
Oxidising properties	Not classified	none	Not classified	Data lacking
Flammability	Not classified	none	Not classified	Data lacking
Other physico-chemical properties *[Add rows when relevant]*	Not classified	none	Not classified	Data lacking
Thermal stability	Not classified	none	Not classified	Data lacking
Acute toxicity	Not classified	none	Not classified	conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	Not classified	none	Not classified	conclusive but not sufficient for classification
Repeated dose toxicity	Not classified	none	Not classified	conclusive but not sufficient for classification
Irritation / Corrosion	Not classified	none	Xi; R36/37/38	Data lacking
Sensitisation	Not classified	none	Not classified	Data lacking
Carcinogenicity	Not classified	none	Not classified	conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	Not classified	none	Not classified	conclusive but not sufficient for classification
Toxicity to reproduction – fertility	Not classified	none	Not classified	conclusive but not sufficient for classification
Toxicity to reproduction – development	R63	none	Not classified	
Toxicity to reproduction – breastfed babies. Effects on or via lactation	Not classified	none	Not classified	conclusive but not sufficient for classification
Environment	N; R50-53	none	N; R51-53	

[1)] Including SCLs

[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Xn, N
R-phrases: R63, R50-53
S-phrases: S(1/2); 60; 61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Dodemorph was included at the latest in the 25th ATP (30-12-1998) (no exact info available, but probably based on data from dodemorph actetate). In 2007, a DAR was prepared by the Netherlands, in the context of the possible inclusion of dodemorph in Annex I of Council Directive 91/414/EEC (addenda to the DAR were prepared in 2008, final addendum in July 2008). At the meeting of experts (PRAPeR 49, June 2008) it was agreed that the observed effects in the toxicological studies that are performed with dodemorph acetate can all be attributed to the dodemorph moiety of dodemorph acetate. The substance was not recently discussed by TCC&L. Dodemorph acetate is not included in Annex VI.

2.2 Short summary of the scientific justification for the CLH proposal

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Dodemorph is currently classified as:

Hazard class: Eye Irrit. 2

STOT SE 3

Skin Irrit. 2

Aquatic Chronic 2

Hazard Statement: H319

H335

H315

H411

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Dodemorph is currently classified as:

Classification: Xi; R36/37/38

N; R51-53

Risk phrases: R36/37/38: Irritating to eyes, respiratory system and skin

R51/53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Safety phrases: S (2): Keep out of the reach of children

S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice

S61: Avoid release to the environment. Refer to special instructions/safety data sheet

Specific Concentration limits: -

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Not relevant for this dossier

2.4.2 Current self-classification and labelling based on DSD criteria

Not relevant for this dossier

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Dodemorph is an active substance in the meaning of Directive 91/414/EEC and according to article 36 of CLP such substances are normally subject to harmonised classification. However, dodemorph acetate is the form in which the active substance is actually placed on the market.

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*

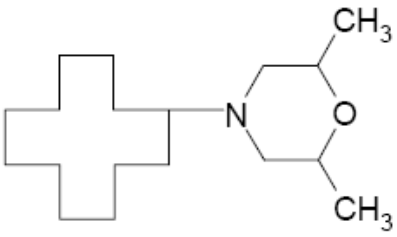
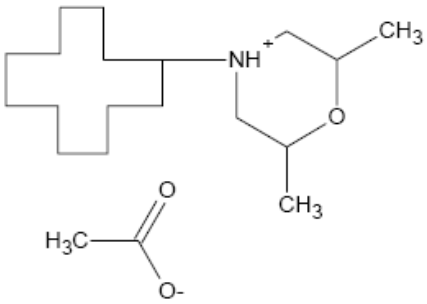


Fig. 2 *– Structural formula of dodemorph acetate*



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.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

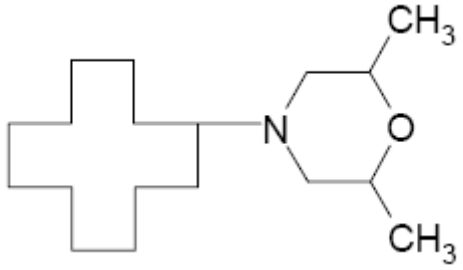
1.1 Name and other identifiers of the substance

Table 5: Substance identity

	Dodemorph
EC number:	216-474-9
EC name:	4-cyclododecyl-2,6-dimethylmorpholine
CAS number (EC inventory):	
CAS number:	1593-77-7
CAS name:	4-cyclododecyl-2,6-dimethylmorpholine
IUPAC name:	*cis/trans*-[4-cyclododecyl]-2,6-dimethylmorpholine
CLP Annex VI Index number:	613-057-00-7
Molecular formula:	$C_{18}H_{35}NO$
Molecular weight range:	281.5

Structural formula:

Dodemorph:



1.2 Composition of the substance

Unknown

The minimum content is 950 g/kg dodemorph acetate in the manufactured material (technical a.i.), on a dry weight basis. Dodemorph acetate is used in all toxicological studies. Nevertheless, dodemorph acetate is never produced as dry material due to the irritant nature, but as a solution (TK), avoiding any potential exposure to worker. The specification for the technical concentrate (TK) is >544g/kg.

It is noted that dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist.

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
4-cyclododecyl-2,6-dimethylmorpholine			All studies are performed with dodemorph acetate. The minimum content of pure active substance (dodemorph acetate) is 950 g/kg in the manufactured material, relative to the dry material. . Dodemorph acetate is never produced as dry material due to the irritant nature, but as a solution (not further specified), avoiding any potential exposure to worker. The specification for the technical concentrate is > 544 g/kg. The active substance is a mixture of cis and trans isomers ranging from a ratio of minimally 50:50 cis:trans and maximally 60:40 cis:trans.

Current Annex VI entry of dodemorph:

Eye Irrit. 2; H319

STOT SE 3; H335

Skin Irrit. 2; H315

Aquatic Chronic 2; H411

or

Xi; R36/37/38

N; R51-53

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential information			The substance does not contain any impurities relevant for classification and labeling

Current Annex VI entry: -

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
Confidential information				

Current Annex VI entry: -

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	non-homogenous solid to a viscous liquid (at 40°C) with a yellow acid aromatic or lemon piquant odour	DAR January 2005 + addendum July 2008	
Melting/freezing point	35 – 48°C	DAR January 2005 + addendum July 2008	
Boiling point	no boiling point could be determined, as probably at 158°C the loss of the acetate as acetic acid is taking place	DAR January 2005 + addendum July 2008	
Relative density	-	DAR January 2005 + addendum July 2008	
Vapour pressure	3.62×10^{-3} Pa at 25 °C	DAR January 2005 + addendum July 2008	
Surface tension	-		
Water solubility	2.29 mg/L at pH 9 to 736 mg/L at pH 5 at 25 °C	DAR January 2005 + addendum July 2008	
Partition coefficient n-octanol/water	4.6	DAR January 2005 + addendum July 2008	
Flash point	73.8 °C	DAR January 2005 + addendum July 2008	
Flammability	autoflammable	DAR January 2005 + addendum July 2008	
Explosive properties	no	DAR January 2005 + addendum July 2008	
Self-ignition temperature	264 °C	DAR January 2005 + addendum July 2008	
Oxidising properties	No	DAR January 2005 + addendum July 2008	
Granulometry	-		
Stability in organic solvents and identity of relevant	-	2008	

degradation products			
Dissociation constant	-		
Viscosity	-		

This table summarizes the physicochemical properties of dodemorph acetate. Physicochemical properties of dodemorph were not available.

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for this type of report.

2.2 Identified uses

Dodemorph acetate is used as a fungicide. The plant protection product is sprayed to the horticultural crops after dilution in water (aqueous dispersion) with an interval between applications of 7-10 days.

Summary of intended uses (a.s. given as dodemorph acetate)

Crop and/or situation (a)	Member State or Country	Product Name	F, G or I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application per treatment			PHI (days)	Remarks (m)
					type (d-f)	conc of as (i)	method kind (f-h)	growth stage & season (j)	number min-max (k)	interval between applications (min-max)	kg as/hL; min-max	water L/ha; min-max	kg as/ha; min-max		
roses	Northern and Southern Europe	Mehltaumittel®	G	powdery mildew, *Sphaeroteca pannosa*	EC	385 g/L	spray (n)	not stated	1-10	7-10	0.1	2000	2	-	

a. For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)
b. Outdoor or field use (F), glasshouse application (G) or indoor application (I)
c. E.g. biting and sucking insects, soil born insects, foliar fungi, weeds

d. E.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

e. GCPF codes - GIFAP Technical monograph No2, 1989
f. All abbreviations used must be explained
g. Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench

h. Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
i. Concentration in g as/kg of g as/L
j. Growth stage at last treatment (BBCH monograph, Growth stages of plants, 1997, Blackwell, ISBN 3-8263-3152-4)
k. The minimum and maximum number of applications possible under practical conditions must be provided.
l. PHI - minimum pre-harvest interval
m. Remarks may include: extent of use / economic importance / restrictions
n. Roses are mostly sprayed manually using handheld knapsack equipment and spray lances.
o. The number of applications should not exceed 2 x 5 sprays per season (total of 10 sprays).

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks
Flammability	Autoflammable auto-ignition temperature 264 °C	
Flash point	73.8 °C	
Explosive properties	No explosive properties: test substance does not explode under the effect of a flame, is not sensitive to shock or friction (EEC A.14).	
Oxidising properties	no oxidizing properties (EEC A.17 (burning pile)	

This table summarizes the results of physico-chemical studies with dodemorph acetate. Physico-chemical studies with dodemorph were not available.

3.1 Physico-chemical properties

3.1.1 Summary and discussion of physico-chemical properties

No data are available for dodemorph.

3.1.2 Comparison with criteria

No data are available for dodemorph.

3.1.3 Conclusions on classification and labelling

No data are available for dodemorph. Therefore, dodemorph should not be classified based on lack of data.

4 HUMAN HEALTH HAZARD ASSESSMENT

Although the subject of the evaluation is dodemorph, all toxicological studies have been performed with the variant dodemorph acetate. Dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist. At the meeting of experts (PRAPeR 49, June 2008) it was agreed that the observed effects can all be attributed to the dodemorph moiety of dodemorph acetate. The values obtained in the different investigations are presented in the conclusion as dodemorph acetate as well as corrected for dodemorph content.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No toxikokinetic data are available for dodemorph. However, since dodemorph dissociates in dodemorph and acetate in aqueous solutions as bodily fluids, it is expected that the toxikokinetics for dodemorph in the body are similar to those of dodemorph acetate. Therefore, data for dodemorph acetate are provided below. It is noted that data for dermal absorption can not be used for read across.

4.1.1 Non-human information

Absorption

After oral administration of a single low dose of ^{14}C-labelled dodemorph acetate (10 mg/kg bw) in rats, peak plasma concentrations were reached after 6-8 h, indicating a moderate rate of absorption. Data indicate that at higher doses (1000 mg/kg bw) there is a slower rate of absorption and/or an increased rate of biliary excretion of dodemorph acetate. It is likely that following oral administration part of the radioactivity that is recovered from feces has been absorbed from the gastro-intestinal tract and subsequently excreted in the bile (with possible enterohepatic cycling). However, the fraction of the radioactivity recovered from feces that can be considered to have been orally absorbed cannot be established. Hence the estimate of the percentage oral absorption, solely based on the amounts of radioactivity recovered in urine, expired air and the body, is considered to be 40%.

Distribution

At termination at 96h post oral dosing in rats, in organs, tissues and carcass less than 4% of radioactivity was recovered. Apart from carcass, the highest levels were found in the liver (up to 0.8%).

Metabolism

In the laboratory animal (and human) dodemorph acetate may readily dissociate in dodemorph and acetate. The data indicate that dodemorph acetate is extensively metabolized, either by microflora in the gut or in the body. The data indicate that degradation of the morpholine ring occurs. Analysis of urine and feces samples demonstrated that 6 very polar metabolites were formed. Since identification of the metabolites reported was not possible, no definite metabolic pathway of dodemorph acetate can be deduced.

Excretion

Excretion of radiolabel is rapid following the low dose, with the majority being excreted within 24h after dosing. Following the high dose excretion is somewhat slower, with the majority of radiolabel being excreted within 96-120h. The excretion pattern showed a sex difference, independent of the dose. In males the ratio of urinary: fecal excretion was higher than in females. Males excreted 32-36% of the dose via urine and 49-50% via feces, whereas females excreted 25-28% via urine and 61-66% via feces. This may indicate that in comparison to males, in females less of the administered dose is absorbed and/or more of the compound is excreted through the bile. In both males and females about 7-13 % of radiolabel is excreted in expired air.

4.1.2 Human information

An *in vitro* dermal absorption study with human and rat skin is available. Dodemorph acetate was tested as concentrate (38.5 mg) or as dilution (0.0963 mg in 0.1 ml). The preparations were applied

to the skin samples at a volume of 10 µl/cm^2. Rat skin was more permeable for dodemorph acetate than human skin. Based on the results of this study, absorption values of 2.7% for the concentrate and 20% for the dilution were derived.

4.1.3 Summary and discussion on toxicokinetics

Animal studies with dodemorph acetate indicate a moderate rate of absorption. At higher doses (1000 mg/kg bw) there is a slower rate of absorption and/or an increased rate of biliary excretion of dodemorph acetate. The estimate of the percentage oral absorption, solely based on the amounts of radioactivity recovered in urine, expired air and the body, is considered to be 40%.

The data indicate that dodemorph acetate is extensively metabolized, either by microflora in the gut or in the body, which includes degradation of the morpholine ring. Several very polar metabolites are formed, but they are not identified.

Excretion of radiolabel is rapid following the low dose, with the majority being excreted within 24h after dosing. Following the high dose excretion is somewhat slower, with the majority of radiolabel being excreted within 96-120h. In males the ratio of urinary: fecal excretion was higher than in females.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies (results given as dodemorph acetate)

Method	Results	Remarks
FIFRA guideline 81-1	Oral LD_{50}: 5500 mg/kg bw	Rats
FIFRA guideline 81-1	Oral LD_{50}: > 2000 mg/kg bw	Rats. Supplementary study
FIFRA guideline 81-2	Dermal LD_{50}: > 2000 mg/kg bw	Rabbit
Acute LC50	Inhalation LC_{50} : not determined	Rats. Study not performed

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

A limit test (FIFRA guideline 81-1) with Sprague Dawley rats was performed with a dose level of 5000 mg dodemorph acetate/kg bw (5m/5f). Due to solubility problems the actual dose level was probably lower (about 1800 mg/kg bw). Therefore, during the following range finding and main tests the test substance was stirred continuously to ensure that an even suspension was administered to the animals. In the range finding tests, dose levels were 100, 500, 1000, 1500 and 2000 mg/kg bw (1m/1f per group) and 3000 and 4000 mg/kg bw (1m/1f per group). In the main study the dose levels were 4200, 4600 and 5000 mg/kg bw (5m/5f per group).
In the limit test, 4 m/4 f died between 4h and two days after exposure. Clinical signs were unusual locomotion, lethargy, tachypnoea, piloerection and catalepsy. At necropsy haemorrhaging in stomach and small intestine and discolouration of liver and kidneys were observed. In the range finding studies no mortality occurred and only lethargy was observed in animals exposed to 3000 and 4000 mg/kg bw.

In the main study 1m/2f died within one day at 5000 mg/kg bw; 2m/1f died within one day at 4600 mg/kg bw; 1f died within 4 h at 4200 mg/kg bw. Lethargy, tachypnoea, catalepsy, and nostril discharge were observed at all dose levels in the main test. Prostration was observed at 5000 mg/kg bw. Most animals that died lost weight. Weight gain was observed in the surviving animals but total gain was lower than observed in the range finding study (dose levels 100 – 2000 mg/kg bw). Haemorrhaging in stomach and small intestine and discolouration of liver, thymus and kidneys were found. Further dark red foci scattered throughout the thymus were found at 5000 mg/kg bw and red fluid in abdominal cavity at 4600 mg/kg bw.

The oral LD 50 value for dodemorph acetate is > 5000 mg/kg bw (95% confidence limits: 4800 – 6300 mg/kg bw), equivalent to > 4100 mg/kg bw dodemorph.

In a second oral toxicity study with Sprague Dawley rats (FIFRA guideline 81-1), dose levels were 1600, 2000, 2500, 3200, 4000, 5000 and 6400 mm^3 dodemorph acetate/kg bw (10m/10f per group), given by gavage as a 20 or 30% aqueous emulsion (v/v) with gum tragacanth.

Mortality rate was 0, 1, 1, 1, 6, 7 and 8 for males and 0, 0, 5, 7, 9, 10, and 10 for females at 1600, 2000, 2500, 3200, 4000, 5000, and 6400 mm^3/kg, respectively. The highest mortality rate was observed within 48 hours after exposure. About half of the male animals died at a dose level of 4000 mm^3/kg bw (equivalent to ≈ 3944 mg/kg bw) and half of the female animals at 2500 mm^3/kg bw (equivalent to ≈ 2465 mg/kg bw).
At 1600 mm^3/kg only slight dyspnoea and apathy were observed. Clinical signs at the higher dose levels were dyspnoea, diarrhoea and titubation (unsteady gait). Necropsy findings were haemorrhagic gastritis and serosanguineous incrustation of nostrils.
LD50 values were not calculated.

4.2.1.2 Acute toxicity: inhalation

An acute inhalation study was not presented in the DAR. In the PRAPeR Expert Meeting 49, it was concluded that based on the physical chemical properties of the substance (high viscosity) and its corrosivity a valid inhalation study could not be carried out and was also not necessary. However, it should be noted that the data from the irritation/corrosion study with dodemorph acetate cannot be used for read across to dodemorph (see 4.4.1.3).

4.2.1.3 Acute toxicity: dermal

A limit test was performed with a dose level of 2000 mg dodemorph acetate/kg bw (5m/5f per group). The semi-solid substance was applied two layers thick onto about 10% of the body surface, and covered with gauze patches. After the exposure period of 24h the skin was rinsed with 0.9% sodium chloride.

There was no mortality, nor were signs of toxicity observed. In all animals the skin site was found to be necrotic from day 1 throughout the 14 days observation period.

The dermal LD50 value for dodemorph acetate is > 2000 mg/kg bw, equivalent to > 1640 mg/kg bw dodemorph.

4.2.1.4 Acute toxicity: other routes

-

4.2.2 Human information

No data are available

4.2.3 Summary and discussion of acute toxicity

No data regarding acute oral, dermal and inhalation toxicity are available for dodemorph. Since dodemorph acetate readily dissociates in dodemorph and acetate in water, the results of the oral studies with dodemorph acetate can be used for read across to dodemorph. An acute inhalation exposure study with dodemorph acetate could not be performed.

Dodemorph acetate is considered to be corrosive. However, it should be noted that the data from the acute dermal study and the irritation/corrosion study with dodemorph acetate cannot be used for read across to dodemorph.

4.2.4 Comparison with criteria

The oral and dermal LD50 values of dodemorph acetate are above the cut of limits of the DSD and CLP criteria (LD50 ≤ 2000 mg/kg bw; dermal LD50 ≤ 2000 mg/kg bw).

4.2.5 Conclusions on classification and labelling

No data are available for dodemorph. The data of the oral toxicity study with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. Therefore, dodemorph does not need to be classified for acute oral toxicity.

However, it should be noted that the data from the acute dermal study and the irritation/corrosion study with dodemorph acetate cannot be used for read across to dodemorph. Dodemorph should therefore not be classified for acute inhalation or dermal toxicity, due to a lack of data.

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No data are available for dodemorph.

In the oral toxicity studies with dodemorph acetate, some toxic effects were observed. However, all these effects are considered to be resulting in lethality at increasing doses.

In the dermal toxicity study with dodemorph acetate, no systemic toxic effects were observed.

An acute inhalation exposure study with dodemorph acetate could not be performed.

4.3.2 Comparison with criteria

No data are available for dodemorph.

According to the CLP Regulation, substances should be classified for STOT SE when:

- They produce significant toxicity in animals (relevant for humans) or humans following single exposure: Cat 1
- They have the potential to be harmful to animals (relevant for humans) or humans following single exposure: Cat 2
- They have transient narcotic effects or cause transient respiratory tract irritation: Cat 3

Dodemorph acetate does not fulfil these criteria.

4.3.3 Conclusions on classification and labelling

Data from the oral toxicity study with dodemorph acetate can be used for read across. The results do not require classification for STOT SE. It should be noted that the data from the acute dermal toxicity study and the irritation/corrosion study with dodemorph acetate can not be used for read

across to dodemorph. Therefore, dodemorph should not be classified for STOT SE, due to a lack of data. The current classification with STOT-SE 3; H335 should therefore be removed.

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.

4.4 Irritation

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks
OECD 404	Severe oedema 24 hours after patch removal. Slight oedema at 48h, very slight oedema at 72h. No oedema 7 days after patch removal. Moderate to severe erythema from 24 up to 72h. Well-defined erythema at 7 days. Necrosis from day 2 to day 7.	Study performed with dodemorph acetate.

4.4.1.1 Non-human information

A skin irritation study was performed in accordance with OECD 404.

The intact, clipped dorsal trunk of one female rabbit was moistened with water after which one water moistened gauze pad containing a single dose of 0.5 g dodemorph acetate (purity 98.2%), and one water moistened control patch were held for 4-hours under semi-occlusive bandage. Observations were performed 1, 24, 48, 72h and 7 days after patch removal.

Severe oedema was noted 24 hours after patch removal. This reduced to slight oedema at 48h and very slight oedema at 72h. No oedema was present 7 days after removal of the patch. Moderate to severe erythema was noted from 24 up to 72h. Well-defined erythema was still present at 7 days. A dark necrotic area was evident from day 2 to day 7 at which point it was decided to terminate the study.

4.4.1.2 Human information

No data are available

4.4.1.3 Summary and discussion of skin irritation

Based on the observed necrotic area, dodemorph acetate is considered corrosive to the skin. Dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist. The solubility of dodemorph acetate is 2.29 mg/L at pH 9 to 736 mg/L at pH 5 at 25 °C (Table 9). The corrosive effects of dodemorph acetate are probably due to the quaternary ammonium ion that is formed at pH < 10.5. Further, the amount of water is limited in an irritation test (wetted skin). When dodemorph is dissolved this will result in an increase of the pH due to the formation of dodemorph-H+ and OH-. The increase in pH limits the solubility and the formation of the quaternary ammonium ion. The concentration of the active form is therefore probably lower when dodemorph is applied than when dodemorph acetate is applied. Therefore, the data of this study can not be used for read across to dodemorph. Due to a lack of data, it remains unknown whether dodemorph is irritating to the skin or corrosive.

4.4.1.4 Comparison with criteria

No data are available for dodemorph.

4.4.1.5 Conclusions on classification and labelling

The current classification for dodemorph is R38 (DSD) or Skin irrit. 2 (CLP). Since there are no data available for dodemorph, it is quite probable that this classification is based on studies with dodemorph acetate. However, the data of the irritation study can not be used for read across to dodemorph. Therefore, dodemorph should not be classified for skin irritation, due to a lack of data. The current classification should therefore be removed.

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.

4.4.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks
FIFRA guideline 81-4	*severe eye irritation*	*rabbits*

4.4.2.1 Non-human information

An eye irritation study was performed in accordance with FIFRA guideline 81-4**.**

An amount of 0.1 ml of undiluted dodemorph acetate (purity 99.6%) was placed in the conjunctival sac of the right eye of 3 rabbits (sex unknown). After an exposure period of 24 h, the eye was rinsed with deionised water in order to remove the test compound. Observations were performed 1, 24, 48, 72 hours, 7, 14 and 21 days after instillation.

Table 14: Eye irritation scores according to Draize scheme

	1h	24h	48h	72h	7d	14d	21d
Cornea	2/2/2	3/2/3	3/2/3	3/2/3	3/3/3	3/3/2	4/4/3
Iris[1]	-/-/-	2/-/-	2/2/2	2/2/2	-/-/-	2/2/1	-/-/1
Redness	3/3/3	3/3/3	3/3/3	3/3/3	2/2/1	3/3/2	2/3/2
Chemosis	4/4/4	4/4/4	4/4/4	4/4/4	3/4/2	3/4/1	2/2/1
Discharge	3/3/3	3/3/3	3/3/3	3/3/3	3/3/2	3/3/1	3/3/1

[1] iris obscured by corneal opacity

4.4.2.2 Human information

No data are available

4.4.2.3 Summary and discussion of eye irritation

Dodemorph acetate produced severe eye irritation in rabbits, which persisted throughout the 21 days observation period. Dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist. The solubility of dodemorph acetate is 2.29 mg/L at pH 9 to 736 mg/L at pH 5 at 25 °C (Table 9). The corrosive effects of dodemorph acetate are probably due to the quaternary ammonium ion that is formed at pH < 10.5. Further, the amount of water is limited in an irritation test (fluid layer on eye). When dodemorph is dissolved this will result in an increase of the pH due to the formation of dodemorph-H+ and OH-. This limits the solubility and the formation of the quaternary ammonium ion. The concentration of the active form is therefore probably lower when dodemorph is applied than when dodemorph acetate is applied. Therefore, the data of this study can not be used for read across to dodemorph. Due to a lack of data, it remains unknown whether dodemorph is irritating to the eye.

4.4.2.4 Comparison with criteria

No data are available for dodemorph.

4.4.2.5 Conclusions on classification and labelling

The current classification for dodemorph is R36 (DSD) or Eye Irrit. 2 (CLP). Since there are no data available for dodemorph, it is quite probable that this classification is based on studies with dodemorph acetate. However, the data of the eye irritation study can not be used for read across to dodemorph. Therefore, dodemorph should not be classified for eye irritation, due to a lack of data. The current classification should therefore be removed.

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.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

No data are available

4.4.3.2 Human information

No data are available

4.4.3.3 Summary and discussion of respiratory tract irritation

4.4.3.4 Comparison with criteria

No data are available for dodemorph.

4.4.3.5 Conclusions on classification and labelling

Currently, dodemorph is classified as R37 (DSD). Since there are no data available for dodemorph, it is quite probable that this classification is based on studies with dodemorph acetate. However, the data of the irritation study can not be used for read across to dodemorph. Therefore, dodemorph should not be classified for respiratory irritation, due to a lack of data. The current classification should therefore be removed.

4.5 Corrosivity

4.5.1 Non-human information

A skin irritation study with dodemorph acetate was performed in accordance with OECD 404. The results of this study are also relevant for the endpoint corrosivity. For details please refer to Section 4.4.1 (skin irritation) of this document.

4.5.2 Human information

No data are available.

4.5.3 Summary and discussion of corrosivity

Based on the observed necrotic area, dodemorph acetate is considered corrosive. Dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist. The corrosive effects of dodemorph acetate are probably due to the quaternary ammonium ion that is formed at pH < 10.5. It is possible that the quaternary ammonium ion is not, or to a lesser extent, formed from dodemorph, due to the limited moistness of the skin, resulting in different forms. Therefore, the data of this study can not be used for read across to dodemorph. Due to a lack of data, it remains unknown whether dodemorph is irritating to the skin or corrosive.

4.5.4 Comparison with criteria

No data are available for dodemorph

4.5.5 Conclusions on classification and labelling

The data of the irritation study can not be used for read across to dodemorph. No data were available for dodemorph. Dodemorph can therefore not be classified for corrosion, due to a lack of data.

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks
OECD 406	positive	guinea pigs

4.6.1.1 Non-human information

A maximisation study was performed in accordance with OECD 406. Female guinea pigs (5 controls, 10 test animals were treated with dodemorph acetate (purity 94%). A 1% concentration was selected for the intra dermal injections on day 1 and a 20% concentration was selected for the

topical induction exposure on day 8 (48 h exposure). The control animals were treated with the vehicle corn oil. On day 21 all animals were challenged with a 5% (non-irritating) concentration (24h exposure). The treated sites were assessed for challenge reactions 24 and 48h after patch removal.

Skin reactions were observed in both the control and treated group. At the 48 h readings 5 animals of the test group showed higher readings (score 2) than those in the control group. Therefore, at least 50% of the animals showed a sensitising reaction. In view of the increased incidence and intensity of the responses in the treated group as compared to the control group, it is considered that dodemorph acetate induces sensitisation.

Table 16: Irritation scores GPMT

Challenge reading	Control group	Test group
24h reading	1/0/0/0/2 (40%)	1/0/2/2/0/0/0/2/2/2 (60%)
48h reading	0/0/0/0/1 (20%)	0/2/1/2/1/1/2 s/1/2/2 (90%)

s = eschar formation

4.6.1.2 Human information

No information available.

4.6.1.3 Summary and discussion of skin sensitisation

In a GPMT test with dodemorph acetate >30% of the test animals showed a more positive response than the control animals at the 48h reading. Dodemorph acetate has a salt like structure which in aqueous environments consists of dodemorph-H+ and Ac- at pH < 6.5 or dodemorph and Ac- at pH > 10.5. At in-between pH values (pH 6.5-10.5) both forms of dodemorph exist. The sensitising effect of dodemorph acetate may be due to the quaternary ammonium ion that is formed at pH < 10.5. It is possible that the quaternary ammonium ion is not or to a lesser extent, formed from dodemorph, because the substance is applied in oil during the induction fase of the GPMT. The amount of the active form may therefore differ after application of dodemorph or dodemorph acetate. Therefore, the data of this study can not be used for read across to dodemorph. Due to a lack of data, it remains unknown whether dodemorph is sensitising to the skin.

4.6.1.4 Comparison with criteria

No data are available for dodemorph.

4.6.1.5 Conclusions on classification and labelling

Since the data of the sensitisation study can not be used for read across to dodemorph, dodemorph cannot be classified for skin sensitisation, due to the absence of data.

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.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

No information available.

4.6.2.2 Human information

No information available.

4.6.2.3 Summary and discussion of respiratory sensitisation

4.6.2.4 Comparison with criteria

4.6.2.5 Conclusions on classification and labelling

No classification proposed due to a lack of data.

4.7 Repeated dose toxicity

Table 17: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks
21 days dermal study, no guideline	NOAEL (local): 12 mg/kg bw/day (~ dodemorph: 10 mg/kg bw/day). NOAEL (systemic) 60 mg/kg bw/day (~ dodemorph: 49 mg/kg bw/day).	Rabbit, 0, 2.4, 12 and 60 mg/kg bw/day
28 days diet study, no guideline	No toxicologically relevant effects were observed	Rats, 0, 50 and 100 mg/kg bw/day
28 days gavage study, no guideline	NOAEL: 40 mg/kg bw/day (~ dodemorph: 33 mg/kg bw/day). LOAEL: 80 mg/kg bw based on vomiting and salivation	Dog, 0, 40, 80 and 160 mg/kg bw/day
90 days diet study, no guideline	mild increase in relative liver weight in females top dose. NOAEL: 80 mg/kg bw	Rat, 0, 20, 40 and 80 mg/kg bw/day
90 days diet study, OECD 408	increased agitated, aggressive and nervous behaviour. Decreased food intake, increased relative liver weight (female), with minimal centrilobular hypertrophy. NOAEL: 79 mg/kg bw	Rat, 0, 20, 79 and 229 mg/kg bw/day for males and 0, 23, 94 and 259 mg/kg bw/day for females
90 days diet study, no guideline	vomiting and salivation, reduced body weight and food intake. Increased liver weight, increased levels of enzymes indicative of liver damage, pale liver, degenerative changes and fatty degeneration. NOAEL: 32 mg/kg bw	Dog, 0, 32, 79 and 187 mg/kg bw/day for males and 0, 33, 79 and 194 mg/kg bw/day for females
1 year oral study, OECD 452	vomiting, salivation and effects on fecal excretion, decreased body weight and food intake, bile duct hyperplasia, associated with marked peribiliary fibrosis, gastric lesions NOAEL: 10 mg/kg bw	Dog, 0, 10, 25 or 62.5 mg/kg bw/day
18 months diet study, OECD 451	Decreased body weight and food intake, increased relative liver weight, accompanied by minimal histological changes in the liver at the high dose NOAEL: 45 mg/kg bw	Mouse, 0, 45, 152 and 455 mg/kg bw/day for males and 0, 55, 184 and 545 mg/kg bw/day for females
2 year diet study, OECD 453	Decreased food intake, increased relative organ weights, not accompanied by macroscopic or microscopic changes (except for liver). NOAEL: 45 mg/kg bw	Rats, 16, 55 and 166 mg/kg bw/day for males and 0, 21, 73 and 222 mg/kg bw/day for females)

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

In a 28 day study (pre-guideline), dietary treatment of rats with dodemorph acetate at doses of 500 and 1000 ppm, (equivalent to about 50 and 100 mg/kg bw/day) did not cause toxicologically relevant effects.

In a 28 day study (pre-guideline), beagle dogs (3/sex/dose) received daily oral (gavage) administrations (distributed in 2 single gifts) of dodemorph acetate (in 1% aqueous methylcellulose-gel 300 P) at doses of 0, 40, 80 and 160 mg/kg bw/day. In animals of the 80 and 160 mg/kg bw/day groups vomiting and salivation were observed, with increased frequency and severity at the highest dose. At the high dose, intervals of slight sedation and soft stools were observed. Food consumption was decreased and the animals lost weight (not specified for sex) in the highest dose group, in particular during the first 2 weeks of treatment. A statistically significant increase in absolute and relative liver weight (data of males and females combined) was observed at 160 mg/kg bw/day. No other treatment-related effects were observed.

In a 90 day study (pre-guideline), Sprague Dawley rats (20/sex/dose) received dodemorph acetate in the diet at 0, 400, 800 or 1600 ppm (equivalent to 0, 20, 40 and 80 mg/kg bw/day). Dietary treatment of female rats with dodemorph acetate caused a mild increase in relative liver weight (12%) at 1600 ppm. However, since these effects were small and not accompanied by histopathological effects, it is not considered in the establishment of the NOAEL. Therefore, the NOAEL in this study is 1600 ppm, equivalent to 80 mg/kg bw/day (equivalent to dodemorph: 66 mg/kg bw/day), i.e. the highest dose tested.

In a 90 day study according to OECD 408, Sprague Dawley rats (10/sex/dose) received dodemorph acetate in the diet at 0, 300, 1200 or 3600 ppm (equal to 0, 20, 79 and 229 mg/kg bw/day for males and 0, 23, 94 and 259 mg/kg bw/day for females). Males of the 3600 ppm group displayed increased agitated, aggressive and nervous behaviour. These signs were observed toward the end of the study. The weekly detailed clinical observations revealed no treatment-related effects. In the functional observational battery and motor activity test no treatment-related clinical effects were observed. Body weight (females) and body weight gain (males and females) were significantly reduced in animals of the high dose group. Food consumption was significantly decreased in males (7-10%) and females (10-27%) of the high dose group. Females of the 3600 ppm group had an increased relative liver weight (17%). Histopathological examination revealed minimal centrilobular hypertrophy in some of the females in this group. In males of the high dose group a 16% reduction (not statistically significant) in relative prostate weight was observed. Since no histopathological effects in the prostate were found, and this finding was not observed in other studies, the reduction in relative prostate weight was considered not toxicologically relevant. The NOAEL was 1200 ppm, equal to 79 mg/kg bw/day (equivalent to dodemorph: 65 mg/kg bw/day).

In a 90 day study (no guideline), Beagle dogs (3/sex/dose) received dodemorph acetate in the diet at 0, 1000, 2500 or 6250 ppm (equal to 0, 32, 79 and 187 mg/kg bw/day for males and 0, 33, 79 and 194 mg/kg bw/day for females). Food was provided in 2 daily portions. In animals of the 2500 ppm group vomiting and salivation were observed, in general only after the first feeding of the day. Similar effects, with increased severity, were observed in the 6250 ppm group. At this dose, these effects were observed after both daily feedings. From the 3rd week onwards vomiting subsided markedly, but could still be observed occasionally. Due to the vomiting test substance may be lost. At 2500 and 6250 ppm, intervals of sedation were observed. At 6250 ppm the animals lost weight. Food consumption was dose-dependently reduced (not specified for sex). Clinical chemistry showed increased levels of enzymes indicative of liver damage at 2500 and 6250 ppm. Absolute and relative liver weights (not specified for sex) were dose-dependently increased at the mid and high dose. At these doses macroscopy demonstrated pale liver. Histological examination revealed

degenerative changes and fatty degeneration. The incidence and severity increased with dose (degenerative changes: moderate in 5/6 animals of the mid dose and 1/6 animals of the high dose, marked in 1/6 animals of the mid dose and 5/6 animals of the high dose; fatty degeneration: moderate in 1/6 animals of the low dose, 2/6 animals of the mid dose and 2/6 animals of the high dose, marked in 3/6 animals of the high dose). NOAEL is 1000 ppm, equal to 32 mg/kg bw/day (equivalent to dodemorph: 26 mg/kg bw/day).

In a 1 year study according to OECD 452, Beagle dogs (4/sex/dose) received oral (capsule) administrations of dodemorph acetate at 0, 10, 25 or 62.5 mg/kg bw/day. One female of the high dose group was killed on day 43 for ethical reasons. Necropsy demonstrated a poor general condition and pale liver. In this animal blood levels of liver enzymes were increased, consistent with the degenerative changes in the liver observed microscopically (capsular fibrosis, bile duct hyperplasia, peribiliary fibrosis of portal tracts, small foci of hepatocellular necrosis in subcapsular areas, sinusoidal dilatation of liver parenchyma and vacuolar degeneration mainly in centrilobulat hepatocytes, iron pigment in macrophages entrapped in the capsular fibrosis). In the other animals, dose dependent increases in the incidence and severity of vomiting, salivation and effects on fecal excretion were observed at the mid and high dose groups. Vomiting was already observed in the first week of treatment. Due to the vomiting test substance may be lost. The vomiting and salivation observed in the low dose animals only occurred sporadically and was not considered to be toxicologically significant. In the high-dose males body weight, body weight gain and food consumption were decreased as compared to controls. Occasional haematological changes were considered incidental. At 13, 26 and 52 weeks, clinical chemistry showed dose-dependently increased levels of enzymes indicative of liver damage at 62.5 mg/kg bw/day; the increase at 25 mg/kg bw/d was only slight and not consistent over time (see Table 6.3.3-4b). Absolute and relative liver weights tended to be increased at all dose levels, although there was no clear dose-response relationship. At the mid and high doses microscopical examination demonstrated bile duct hyperplasia, associated with marked peribiliary fibrosis. At these doses macroscopical and microscopical examination revealed gastric lesions in some animals. The NOAEL is 10 mg/kg bw/day (equivalent to dodemorph: 8 mg/kg bw/day).

In an 18 month study according to OECD 451, Crl:CD-1 (ICR) BR VAF/plus mice (50/sex/dose) were exposed to dodemorph acetate in the diet at 0, 300, 1000 or 3000 ppm (equal to 0, 45, 152 and 455 mg/kg bw/day in males and 0, 55, 184 and 545 mg/kg bw /day in females). Body weight gain was reduced at the mid and high dose. Slight reductions in food consumption were observed in the high dose group. Relative liver weight was significantly increased in males of the mid-dose group, and males and females of the high-dose groups. These liver weight effects were accompanied by minimal histological changes in the liver at the high dose. Occasionally statistically significant increases in other organ weights relative to body weights were observed. The changes in organ weights were not accompanied by macroscopic or microscopic changes, and the organ weights relative to brain weight were not affected. Therefore, these changes are considered secondary to the decreased body weights in these animals, and considered not a direct effect of treatment. Females of all treatment groups had a lower relative spleen weight than the control animals. However, these effects were not dose dependent, were not found in males, and may be related to a high spleen weight in the control females. NOAEL in this study is 300 ppm, equal to 45 mg/kg bw/day (equivalent to dodemorph: 37 mg/kg bw/day).

In a 2 year study according to OECD 453, Sprague Dawley rats (50/sex/dose) were exposed to dodemorph acetate in the diet at 0, 300, 1000 or 3000 ppm (equal to 0, 16, 55 and 166 mg/kg bw/day in males and 0, 21, 73 and 222 mg/kg bw /day in females). Small but statistically significant decreases in food consumption were observed in the high dose animals throughout the duration of the study. The sporadic changes observed in haematological, clinical chemistry and urinalysis were

considered incidental and not treatment-related. At the interim and terminal kill, in animals of the high dose groups statistically significant increases in organ weights relative to body weights (males: liver (11%) and testes (11%); females: adrenals (16%), kidneys (15%), liver (26%) and lung (20%) were observed. The changes in organ weights were not accompanied by macroscopic or microscopic changes (except for liver), were not consistent when comparing 12 and 24 month data or only occurred in one sex. Moreover, the organ weights relative to brain weight were not affected. Therefore, these changes are considered secondary to the decreased body weights in these animals (males -8%; females -20%), and considered not a direct effect of treatment. In the liver of the 3000 ppm group increased incidences of foci of cellular alterations and regenerative hyperplasia were observed. Hyperplasia was also observed in the females of the 1000 ppm group at the interim kill. In the lungs dose dependent increases in incidences of white-grey foci, macrophage infiltration and granulomatous inflammation of the lung were observed. According to the study author, these effects, and the presence of fluid and plant material in the lungs of both control and treated animals are attributable to the inadvertent inhalation of foreign material, and are therefore considered not related to oral exposure to dodemorph acetate. The NOAEL is 1000 ppm, equal to 55 mg/kg bw/day (equivalent to dodemorph: 45 mg/kg bw/day).

4.7.1.2 Repeated dose toxicity: inhalation

No data available.

4.7.1.3 Repeated dose toxicity: dermal

In a 21 days (pre-guideline) study, New Zealand White rabbits (3/sex/dose), with intact or scarified skins, received daily dermal administrations of 3 g/kg bw of a 1% aqueous methylcellulose solution containing 0, 0.08, 0.4 or 2.0% dodemorph acetate for 21 days. These doses are equal to 0, 2.4, 12 and 60 mg/kg bw/day. The test solution was spread over a 15 x 16 cm^2 area (i.e. 240 cm^2), and covered with a rubber flap. Based on an average body weight of 2.7 kg, the local dodemorph acetate doses were 0, 0.027, 0.135 and 0.675 mg/cm^2. Animals of the 2% group showed progressive development of local erythema and oedema and scab formation. Erythema and oedema were first observed after 4 days (intact skin) or 2 days (scarified skin) of treatment, reaching maximum Draize score by day 17 (intact skin) or day 15 (scarified skin). The local skin effects in animals with scarified skin fully recovered during a 21-day recovery period.
No treatment-related systemic effects were observed.

Further dermal repeated dose studies were not performed since:

1. in terms of animal welfare it would be deemed outwith Inveresk severity limits to repeatedly apply a test item known to cause burns.

2. any results gained from such a study would be difficult to interpret i.e. it would be very difficult to determine which were systemic toxicity effects and which were due to distress inflicted on the animal by the corrosive material.

4.7.1.4 Repeated dose toxicity: other routes

4.7.1.5 Human information

4.7.1.6 Other relevant information

4.7.1.7 Summary and discussion of repeated dose toxicity

No data regarding repeated oral, dermal and inhalation toxicity are available. Since dodemorph acetate readily dissociates in dodemorph and acetate in water, the results of the oral studies with dodemorph acetate can be used for read across to dodemorph.

It should be noted that the data from the dermal study with dodemorph acetate cannot be used for read across to dodemorph, due to the limited moistness of the skin.

Subacute and semichronic oral studies with dodemorph acetate in the rat and the dog were available. In these studies the main targets for dodemorph acetate were body weight and 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 semichronic 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 ALAT and AP indicate that dodemorph acetate induced hepatocellular damage and cholestasis. The 1-year study in the dog provided the lowest NOAEL (10 mg/kg bw/day, equivalent to 8.2 mg dodemorph/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, in the dog study 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.

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

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

See paragraph 4.7.1.7

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

No data are available for dodemorph. However, the data of the oral toxicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. See below. It should be noted that the data from the dermal study with dodemorph acetate cannot be used for read across to dodemorph.

According to DSD, the cut off values for classification as causing danger of serious damage to health by prolonged exposure are:

<50 mg/kg bw/day in a 90 day oral study (or 150 mg/kg bw/day in a 28 day oral study)

<100 mg/kg bw/day in a 90 day dermal study (or 300 mg/kg bw/day in a 28 day dermal study)

Dodemorph acetate does not fulfil the criteria for classification for oral repeated dose toxicity as the LOAEL in the 90-day studies was clearly above the cut-off value.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

No data are available for dodemorph. The data of the oral toxicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. Dodemorph acetate does not fulfil the criteria for classification for oral repeated dose toxicity. Therefore, also dodemorph does not need to be classified for repeated oral toxicity.

It should be noted that the data from the dermal study with dodemorph acetate cannot be used for read across to dodemorph. In addition, no data are available for repeated inhalation toxicity. Dodemorph should therefore not be classified for repeated inhalation or dermal toxicity, due to a lack of data.

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, **50** & **100** 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, **70/63**, 140/123 & 271/238 mg/kg bw/day for males/females)	None	None
Rat, 90 days, diet	0, **20**, **40** & **80** mg/kg bw/day (approx)	None	None
Rat, 90 days, diet (OECD 408)	0, **20/23**, **79/94**, & 229/259 mg/kg bw/day for males/females (approx)	None	None
Rat, 70+ days, diet two-generation study; OECD 416	0, **21**, **64** & 194 mg/kg bw/day	None	None
Rat, 2-year, diet OECD 453	0, **16/21**, 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, **40**, **80** & 160 mg/kg bw/day	None	Vomiting & salivation at 80 mg/kg bw/day
Dog, 90 days diet	0, **32/33**, **79/79** & 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, **10**, **25** & 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.
Studies involving dermal exposure			
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.

Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.7.2 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

See paragraph 4.7.1.7

4.7.3 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

No data are available for dodemorph. However, the data of the oral toxicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. See below. It should be noted that the data from the dermal study with dodemorph acetate cannot be used for read across to dodemorph.

According to CLP, the cut off values for classification for STOT RE are:

<100 mg/kg bw/day in a 90 day oral study

<200 mg/kg bw/day in a 90 day dermal study

Dodemorph acetate does not fulfil the criteria for classification for oral repeated dose toxicity because the effects at the LOAEL that was just below the cut off value were limited (bile duct hyperplasia without consistent enzymatic changes or significant changes in organ weight).

4.7.4 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

No data are available for dodemorph. The data of the oral toxicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. Dodemorph acetate does not fulfil the criteria for classification for oral repeated dose toxicity. Therefore, also dodemorph does not need to be classified for repeated oral toxicity.

It should be noted that the data from the dermal study with dodemorph acetate cannot be used for read across to dodemorph. In addition, no data are available for repeated inhalation toxicity. Dodemorph should therefore not be classified for repeated inhalation or dermal toxicity, due to a lack of data.

4.8 Germ cell mutagenicity (Mutagenicity)

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Results	Remarks
Ames test, resembles OECD 471	negative	With and without S9
HGPRT, resembles OECD 476	negative	With and without S9
Chromosome aberration in vitro, resembles OECD 473	Results not suitable	With and without S9 Not acceptable
DNA repair assay, in vitro	Results not suitable	With and without S9 Not acceptable
UDS, in vitro	Negative	
Micronucleus test in vivo, resembles OECD 474	Negative	

4.8.1 Non-human information

4.8.1.1 In vitro data

An Ames test according to OECD 471 (unknown purity) was performed with dodemorph acetate, solved in ethanol. Under the test conditions, dodemorph acetate (purity unknown) did not induce point mutations in S. typhimurium (strains 98, 100, 1535, 1537 and 1538).

A HGPRT locus gene mutation test in Chinese Hamster Ovary cells (resembling OECD 476) was performed with dodemorph acetate, solved in DMSO. Cytotoxicity (>50%) in the main test was observed from 0.0464 mg/mL for cells in absence of S9, and at 0.464 mg/mL for cells in presence of S9. A first test was performed with 5 flasks per dose level up to a dose level of 0.215 mg/mL. In this test a borderline increase of mutation rate (15.10-6) was observed at a low dose level in presence of S9 (0.0215 mg/mL). The test was repeated in presence and absence of S9, with an extra dose level. No increased mutation rates were observed in this test.

A chromosome aberration test in Chinese Hamster Ovary cells according to OECD 473 (unknown purity) was performed with dodemorph acetate, solved in ethanol. Complete cytotoxicity in the

main test was observed from 0.11 µL/mL for cells in absence or presence of S9. The slides of these test groups could not be used for cytogenetic analysis because no metaphase cells were observed on the slides. No increased incidence in chromosome aberrations was observed in this test for the remaining dose levels of 0.01 and 0.04 µL/mL. The study is considered not acceptable, due to too many deviations from the guideline (unknown purity, only 2 analysable doses, no additional experiment performed).

A DNA repair assay in E. coli was conducted with dodemorph acetate. In the first test the assay without metabolic activation could not be evaluated because of complete toxicity of the positive control group; in the repeat trial (with an acceptable result in the positive control), the survival indexes were all near or above the survival index for the negative control group. The first test with metabolic activation was negative (only one single observation of lower survival index was observed at 0.01 µL only and this was considered an incidental finding). The repeat test was not valid because of the failure of the positive control to induce a differential survival in the test.

A UDS assay in hepatocytes from male F344 rat (resembling OECD 482) was performed with dodemorph acetate, solved in DMSO. Three replicate cultures were used per dose and 50 cells were scored/replicate. The highest dose level (50 µg/mL) showed a low survival rate (22%) and there were insufficient cells for analysis. The survival rate at 30 µg/mL was 84% and in all lower dose levels 100%. Under the test conditions, dodemorph acetate (purity unknown) did not induce significant changes in the nuclear labelling of primary rat hepatocytes.

4.8.1.2 In vivo data

A mouse micronucleus test resembling OECD 474 was performed with dodemorph acetate.
Single oral exposures of 0, 250, 500, 1000 mg/kg bw were used. Animals of the high dose showed marked toxicity and were in poor general state (irregular respiration, piloerection, apathy, atony, spastic gait and squatting posture). The mid dose group showed irregular respiration and slight excitation, the low dose group only piloerection. No pathological changes at necropsy were observed in any dose group. No significant changes in NCE/PCE ratio were observed.
Animals were sacrificed at 24 h after exposure, and only in the high dose group also after 16 and 48 h. Only 1000 polychromatic cells /animal (instead of 2000) were investigated. However, 10 analysable animals (5m/5f) were used where only 5 are prescribed in OECD 474. No toxicity was observed in the target organ. However, marked signs of systemic toxicity were observed in animals. Therefore, the study is considered acceptable. Under the test conditions, dodemorph acetate did not induce micronuclei in mouse bone marrow cells.

4.8.2 Human information

No data are available.

4.8.3 Other relevant information

4.8.4 Summary and discussion of mutagenicity

No data are available for dodemorph. However, the results of dodemorph acetate can be used for read across, since dodemorph acetate readily dissociates in dodemorph and acetate in aqueous environments.

Dodemorph acetate did not induce gene mutations in either bacterial cells or mammalian cells. A negative result was also found in a test for unscheduled DNA synthesis with rat hepatocytes. An in vitro test in Chinese hamster cells for induction of chromosome aberrations and a DNA repair test in E. coli bacteria were not considered suitable for evaluation. No acceptable in vitro chromosome aberration test was available. However, an in vivo a mouse micronucleus test was negative. Based on all available data it is concluded that dodemorph acetate, and dodemorph are not genotoxic.

4.8.5 Comparison with criteria

If there is evidence from in vitro or in vivo studies (or evidence in humans) that a substance (may) induce heritable mutations in humans, they should be classified for mutagenicity (both according to DSD and CLP). Dodemorph and dodemorph acetate do not fulfil these criteria.

4.8.6 Conclusions on classification and labelling

No data are available for dodemorph. However, the results of dodemorph acetate can be used for read across, since dodemorph acetate readily dissociates in dodemorph and acetate in watery environments. Dodemorph therefore does not need to be classified for mutagenicity.

4.9 Carcinogenicity

Table 19: Summary table of relevant carcinogenicity studies

Method	Results	Remarks
OECD 451	not carcinogenic	Mouse
OECD 453	not carcinogenic	Rat

4.9.1 Non-human information

4.9.1.1 Carcinogenicity: oral

In an 18 month study according to OECD 451, Crl:CD-1 (ICR) BR VAF/plus mice (50/sex/dose) were exposed to dodemorph acetate in the diet at 0, 300, 1000 or 3000 ppm (equal to 0, 45, 152 and 455 mg/kg bw/day in males and 0, 55, 184 and 545 mg/kg bw /day in females).

A number of neoplastic lesions were observed in control and treated animals. These were of a type and incidence that are commonly observed in mice of this strain, age and sex. Statistical analysis showed no dose-related trend. Moreover, the incidences of neoplastic lesions were within the range of historical control data of Charles River Laboratories. Therefore they were considered of a spontaneous nature and not treatment-related.

In a 2 year study according to OECD 453, Sprague Dawley rats (50/sex/dose) were exposed to dodemorph acetate in the diet at 0, 300, 1000 or 3000 ppm (equal to 0, 16, 55 and 166 mg/kg bw/day in males and 0, 21, 73 and 222 mg/kg bw /day in females). In the liver of the 3000 ppm group increased incidences of foci of cellular alterations and regenerative hyperplasia were observed. Hyperplasia was also observed in the females of the 1000 ppm group at the interim kill.

The occasional increased incidences in neoplastic lesions in the high dose group fell within the historical range of Charles River Laboratories, and were considered spontaneous and not related to dodemorph acetate treatment. A number of neoplastic lesions were observed in control and treated

animals. These were of a type and incidence that are commonly observed in rats of this strain (see table 21). The incidences of neoplastic lesions were within the range of historical control data of Charles River Laboratories. There was no indication of a treatment-related increase in incidences in number of neoplasms.

Table 20 Group incidences of neoplastic lesions in 2-year oral study in the rat (%)

Dose (ppm)	*0*	*0*	*300*	*300*	*1000*	*1000*	*3000*	*3000*	*dr*
Sex	*m*	*f*	*m*	*f*	*m*	*f*	*m*	*f*	
12 month interim necropsy									
Liver									
- adenoma	*-*	*-*	*-*	*-*	*5.0*	*-*	*-*	*-*	
mammary gland									
- fibroadenoma	*-*	*10.0*	*-*	*-*	*-*	*5.0*	*-*	*15.8*	
thyroid gland									
-follicular cell adenoma	*-*	*-*	*5.0*	*-*	*-*	*-*	*-*	*-*	
pituitary gland									
- adenoma	*5.0*	*-*	*10.0*	*-*	*5.0*	*-*	*-*	*-*	
adrenal gland									
- pheochromocytoma/benign	*5.0*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	
2-year final necropsy									
adrenal gland									
- pheochromocytoma/benign	*-*	*2.0*	*5.9*	*-*	*20.0*	*-*	*4.1*	*-*	
- pheochromocytoma/malignant	*2*	*2.0*	*5.9*	*3.5*	*-*	*-*	*4.1*	*2.0*	
brain									
- granular cell tumor	*-*	*-*	*-*	*-*	*6.3*	*-*	*-*	*2.0*	
duodenum									
-polyp	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*2.3*	
kidney									
- adenoma	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*2.0*	
ovary									
- adenocarcinoma	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*4.2*	
skin									
- basilioma/benign	*-*	*-*	*-*	*-*	*-*	*-*	*4.0*	*-*	
- fibrosarcoma	*-*	*-*	*-*	*-*	*-*	*-*	*2.0*	*-*	
- keratoacanthoma	*-*	*-*	*-*	*-*	*-*	*-*	*2.0*	*-*	
mesenteric lymph node									
- lymphangioma	*2.0*	*-*	*-*	*-*	*-*	*-*	*-*	*2.3*	
pancreas									
- adenoma/islet cell	*4.1*	*4.2*	*11.1*	*-*	*6.6*	*-*	*8.0*	*-*	
pituitary gland									
- adenoma	*42.0*	*67.4*	*58.8*	*85.4*	*64.3*	*80.1*	*48.0*	*80.0*	
thyroid gland									
- adenoma/follicular cell	*4.0*	*2.1*	*-*	*-*	*6.3*	*-*	*2.1*	*4.6*	
uterus									
- sarcoma NOS		*-*		*-*		*-*		*4.0*	
-Schwannoma		*-*		*-*		*-*		*2.0*	
- squamous carcinoma		*-*		*-*		*-*		*2.0*	

Percentages given are based on number of lesions divided by the number of tissues examined.

(For further adverse effects observed in these studies, see paragraph 4.7; repeated dose toxicity)

4.9.1.2 Carcinogenicity: inhalation

No data available

4.9.1.3 Carcinogenicity: dermal

No data available

4.9.2 Human information

No data available

4.9.3 Other relevant information

4.9.4 Summary and discussion of carcinogenicity

No data are available for dodemorph.

In the chronic toxicity studies no tumorigenic potential of dodemorph acetate was identified.

4.9.5 Comparison with criteria

No data are available for dodemorph.

Dodemorph acetate does not fulfil the criteria of DSD and CLP for classification as carcinogenic, since in 2 carcinogenicity studies no tumorigenic potential of dodemorph acetate was identified.

4.9.6 Conclusions on classification and labelling

The data of the oral carcinogenicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. Therefore, dodemorph does not need to be classified for carcinogenicity.

4.10 Toxicity for reproduction

Table 21: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks
One generation, no guideline (range finding study, main study see below)	Parental: reduction in food consumption and body weight gain. Decreased blood cholesterol, increased blood creatinine. No effects on fertility. Offspring: decreased body weight at birth, decreased body weight gain, decreased litter size and reduced viability index	Rat
OECD 416	Parental: reduction in body weight gain, food consumption and blood cholesterol and histological changes in the liver. No effects on fertility. Offspring: decreased body weight at birth, decreased body weight gain, decreased viability and lactation indices.	Rat
OECD 414 (2001)	Maternal: salivation; bw (corrected)↓ Dev: Decreased body weight; skeletal variations	Rat
Developmental toxicity study, no guideline (range finding study, main study see below)	Maternal: top doses: severe toxicity, resulting in 100% implantation loss. Low dose group: reduced body weight and food intake, increased ALT, GGT and cholesterol. Increased post implantation loss, due to late resorptions. Offspring: anasarca, open eye	Rabbit
OECD 414 (1981)	No maternal toxicity. Dev: Early resorptions; post implantation loss; open eye malformation	Rabbit

All studies are performed with dodemorph acetate.

4.10.1 Effects on fertility

4.10.1.1 Non-human information

In a range-finding one-generation reproductive toxicity test in rats (no GLP, no guideline), dodemorph acetate (purity 98.7%) was administered orally in the diet at 0, 600, 1200 and 2400 ppm (equal to 0, 70, 140 and 271 mg/kg bw/day for males and 0, 63, 123 and 238 mg/kg bw/day for females, i.e. compound intake during gestation) to animals of the F0 generation (10/sex/dose). Treatment started at least 42 days before mating and continued until day 21 after birth of the pups. Animals were checked daily for clinical signs and mortality. Food and drinking water consumption and body weight were measured weekly. Females were weighed on days 0, 7, 14 and 20 of gestation. Females and pups were weighed on days 4, 7, 14 and 21 after giving birth. Male and

female reproduction parameters, and pup parameters were determined. Blood of parental animals was sampled for haematology (differential blood smears and reticulocytes were not evaluated) and clinical chemistry.

Table 22 Results from 1-generation reproductive toxicity study (range-finding) in the rat

	Dose (ppm)	0	0	600	600	1200	1200	2400	2400	dr
	Sex	m	f	m	f	m	f	m	f	
F0 animals	Mortality	no toxicologically relevant effects								
	Clinical signs	no toxicologically relevant effects								
	Body weight gain as % change from control -premating -gestation			-4	-9 +1	-3	-11 -11	-18*	-21* -27*	 dr dr
	Food consumption as % change from control -premating during gestation during lactation			-1	-4 -1 -2	-1	-6 -7 -9	-8*	-12* -14* -36*	 dr dr dr
	haematology	no toxicologically relevant effects								
	clinical chemistry - cholesterol - creatinine			-7 +5	-2 +7	-17* +10*	0 +7	-26* +10*	-15* +12*	 dr dr
	Mating, fertility, gestation	no toxicologically relevant effects								
	gestation duration	no toxicologically relevant effects								
F1 pups	Litter size	15.3		15.0		13.6		11.7*		dr
	viability index as % survivors, day 0-4	95		96		95		61*		
	Lactation index as % survivors, day 4-21	99		99		99			95	
	Sex ratio	no toxicologically relevant effects								
	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)	dr
	Pathology									
	- macroscopy	no toxicologically relevant effects								

* significantly different; dr = dose related

Dietary treatment with dodemorph acetate at 1200 and 2400 ppm induced dose-dependent reductions in food consumption and body weight gain in parental males and females. In addition a decrease in blood cholesterol and an increase in blood creatinine were observed, which may be related to the decreased food consumption and body weight. In the 2400 ppm group a decrease in litter size was observed. In the pups of the 2400 ppm group a reduced viability index, a decreased body weight on day 1 and a decreased body weight gain from day 4-21 was observed.

In a 2-generation reproduction toxicity study according to OECD guideline 416, dodemorph acetate (purity 98.7%) was administered orally in the diet at 0, 200, 600 or 1800 ppm (equal to 0, 21, 64 and 194 mg/kg bw/day) to rats (25/sex/dose) of the F0 generation. Treatment started at least 70 days before mating. The F0 animals were mated to produce two litters (F1a and F1b). At day 4 after birth litters were culled, where possible, to 4 males and 4 females. Selected animals from the F1a group were used to produce the F2 generation.
The animals were checked daily for clinical signs. Generally, food consumption and body weights were determined weekly. However, body weights of females were determined on days 0, 7, 14 and 20 of gestation and on days 4, 7, 14 and 21 after giving birth. Food consumption of females was determined for days 0-7, 7-14 and 14-20 of gestation and days 1-4, 4-7 and 7-14 post-partum. Male and female reproduction parameters were determined. Haematology and clinical chemistry were performed on 12 animals/sex/dose from the F0 and F1 parental animals. Litters were examined for number of pups delivered, sex ratio. Pups were checked for viability index (% survival from days 1-

4), lactation index (% survival from days 4-21), body weights, body weight changes, developmental landmarks and behaviour (grip reflex, acoustic startle, pupillary reflex). All pups were examined macroscopically at necropsy. In addition, selected pups were examined microscopically for organ and skeletal findings. For haematology and clinical chemistry, blood from F0 and F1 parental animals was sampled towards the end of the treatment period. At termination the parental animals were killed, necropsied, selected organs were weighed, and the reproductive organs and liver and kidney were histologically examined.

Table 23 Results from 2-generation reproductive toxicity in the rat

	Dose (ppm)	0	0	200	200	600	600	1800	1800	dr
	Sex	m	f	m	f	m	f	m	f	
F0 parents	Mortality	no toxicologically relevant effects								
	Clinical signs	no toxicologically relevant effects								
	Body weight gain as % change from control									
	-premating (F1a)			-1	-2	-1	-2	-13*	-18*	
	-gestation (F1a)				+4		+4		-9	
	Food consumption as % change from control									
	-premating (F1a)			0	0	+1	0	-6	-10*	
	-gestation (F1a)				+4		+4		-7*	
	-lactation (F1a)				-4		-4		-14*	
	haematology	no toxicologically relevant effects								
	clinical chemistry as % change from control									
	- cholesterol			-9	-5	-14	+11	-25*	-11	dr[m]
	Mating, fertility	no toxicologically relevant effects								
	Gestation duration	no toxicologically relevant effects								
	relative organ weight									
	- liver								+8	
	- macroscopy	no toxicologically relevant effects								
	microscopy									
	- minimal hypertrophy periacinar hepatocytes	0/25	0/25	0/25	0/25	0/25	0/25	0/25	13/25*	
F1a,b pups	Litter size	no toxicologically relevant effects								
	Viability index									
	F1a	98		97		98		87*		
	F1b	95		94		95		92		
	lactation index									
	F1a	96		99		99		100		
	F1b	99		98		99		96*		
	Physical development [A]									
	F1a									
	Pinna unfolding	98.2		93.1		89.6		68.4*		dr
	auditory canal opening	100		96.9		95.8		79.3*		
	eye opening	95.1		99.5		91.8		71.4*		
	F1b									
	Pinna unfolding	95.5		82.1		79.7*		53.0*		dr
	auditory canal opening	96.7		94.4		98.4		73.6*		
	eye opening	93.2		90.6		87.4		62.5*		dr
	Sex ratio	no toxicologically relevant effects								
	Body weight (g) day 1									
	F1a	6.6	6.2	6.6	6.3	6.5	6.2	5.9*	5.7*	
	F1b	6.5	6.1	6.5	6.1	6.3	6.1	5.8*	5.5*	
	Body weight gain (g)									
	F1a									
	day 1-4	3.1	2.9	2.8	2.9	2.6	2.5	2.1*	2.1*	dr
	day 4-21	45.7	43.1	44.2	42.2	42.5*	40.2*	34.4*	33.3*	dr
	F1b									
	day 1-4	2.7	2.6	2.7	2.5	2.3	2.2	2.0*	1.8*	dr
	day 4-21	43.3	41.3	41.9	39.4	41.5	39.7	34.5*	32.8*	dr
	macroscopy	no toxicologically relevant effects								
F1 parents	Mortality	no toxicologically relevant effects								
	Clinical signs	no toxicologically relevant effects								
	Body weight gain as % change from control									
	-premating			0	+1	-2	-4	-7*	-6*	dr
	-gestation				0		-7		-19*	dr

	Dose (ppm)	0	0	200	200	600	600	1800	1800	dr
	Sex	m	f	m	f	m	f	m	f	
	Food consumption as % change from control -premating -gestation -lactation			-1	0 +2 -3	0	-1 +2 -3	-6*	-7* -7* -25*	
	clinical chemistry as % change from control - cholesterol			-4	-7	-8	-11	-31*	-16	dr
	Mating, fertility, gestation	no toxicologically relevant effects								
	Relative organ weights	no toxicologically relevant effects								
	macroscopy	no toxicologically relevant effects								
	microscopy - minimal hypertrophy periacinar hepatocytes	0/25	0/25	0/25	0/25	0/25	0/25	0/25	9/25*	
F2 pups	Litter size	no toxicologically relevant effects								
	Sex ratio	no toxicologically relevant effects								
	viability index	96		94		98		79*		
	lactation index	99		99		99		95		
	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*	dr
	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*		
	behavioural tests	no toxicologically relevant effects								
	- macroscopy	no toxicologically relevant effects								

* significantly different; dr = dose related

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

At dietary concentrations of 1800 ppm, in the F0 and F1 parental animals a reduction in food consumption and body weight gain was observed, accompanied by a reduction in blood cholesterol levels. At this dose in the F0 and F1 females an increased incidence in minimal hypertrophy of periacinar hepatocytes was observed. In the high dose group a reduction in absolute kidney weights in males and females and a reduced absolute epididymes weight was observed. However, these findings were considered to be related to the decreased body weight, and not directly related to dodemorph acetate treatment.

As 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 litters (21.4 days) in the 1800 ppm group and the F1b litters (21.6 days) of the 600 ppm 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 placed together for a period of about 16 hours. The birth of the litter was generally evaluated in the mornings in connection with the clinical observation. Apparently, the method of establishing both the start of gestation and the birth of the pups lacks 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.

Based on the effects observed at 1800 ppm the NOAEL for parental toxicity was 600 ppm, equal to 64 mg/kg bw/day (equivalent to dodemorph: 52 mg/kg bw/day).

No treatment-related effects of dodemorph acetate on reproductive function were observed at doses up to and including 1800 ppm, equal to 194 mg/kg bw/day (equivalent to dodemorph: 159 mg/kg bw/day).

4.10.1.2 Human information

No information available.

4.10.2 Developmental toxicity

4.10.2.1 Non-human information

In a developmental toxicity study according to OECD guideline 414, groups of 25 pregnant rats were given dodemorph acetate (purity 98.8%) at a dose of 30, 100 or 300 mg/kg bw per day by gavage on days 6 through 19 of gestation. Controls were treated with vehicle (olive oil). Body weight and food consumption were recorded every second or third day, and the dams were examined daily for clinical signs of toxicity. On gestation day 20 blood was taken from the retro orbital venous plexus of all females (non fasted). Immediately thereafter they were sacrificed and the foetuses were removed from the uterus and dams were examined macroscopically. Blood samples were examined for haematological parameters and clinical chemistry parameters. Apart from uterus and ovaries also the liver was removed; unopened uterus and liver were weighed. Foetuses were removed, weighed, sexed, and observed for gross malformations, then preserved for examination of soft tissue and/or skeletal abnormalities.

Table 24 Results from a developmental toxicity study in rats

	Dose (mg/kg bw per day)	0	30	100	300	dr
Maternal effects	Mortality	no mortality				
	Clinical signs - salivation	0/25	0/25	14/25	25/25	dr
	Pregnant animals	25	22	21	21	
	Body weight at GD20 (g)	284	276	280	269*	
	Corrected body weight gain in grams (% of control) [1]	33.7	31.6 (-6)	26.0 (-23)	20.4* (-31)	dr
	Food consumption GD 6-13 as % of control		91 %	79%	53%*	dr
	Haematology - MCV (FL) - MCHC (mmol/L) - platelet (giga/L)	 56.7 20.01 757	 56.6 20.11 767	 56.1 20.37 760	 55.3* 20.67* 860*	 dr
	Clinical chemistry - Na (mmol/L) - Cl (mmol/L) - Ca (mmol/L) - total Bilirubin (µmol/L) - triglycerides (mmol/L)	 140.3 101.1 2.71 1.37 5.01	 140.2 100.4 2.77 1.22 6.15	 139.7 100.5 2.73 0.93 7.37	 138.0* 98.1* 2.79* 0.37* 11.06*	 dr dr
	Organ weights as % change from control - liver (a/r)		 -2/0.5	 -1/1	 11/17*	
	Abortions	no abortions				
	Gravid uterine weight	no toxicologically relevant effects				
	Corpora lutea	no toxicologically relevant effects				
	Pathology	no toxicologically relevant effects				
Litter response	Live foetuses	no toxicologically relevant effects				
	Foetal weight as % of control		100	103	94	
	Pre implantation loss	no toxicologically relevant effects				
	Post implantation loss	no toxicologically relevant effects				
	resorptions	no toxicologically relevant effects				
Foetus examination	No. of foetuses	no toxicologically relevant effects				
	No. of dead foetuses	no dead foetuses				
	Sex ratio (f/m)	no toxicologically relevant effects				
	Malformations	no toxicologically relevant effects				
	Variations a] Visceral deviations [2] litter incidences + (%)					

	Dose (mg/kg bw per day)	0	30	100	300	dr
	- total visceral variations	1 (4)	4 (18)	7* (33)	5 (24)	
	- dilated renal pelvis	1 (4)	4 (18)	7* (33)	5 (24)	
	b] Skeletal deviations [3] litter incidences + (%)					
	- total skeletal variations	25 (100)	22 (100)	21 (100)	21 (100)	
	- misshapen sternebra	16 (64)	18 (82)	16 (76)	19* (90%)	
	- unossified sternebra	6 (24)	5 (23)	4 (19)	11* (52)	
	- incomplete oss. of lumbar arch	0 (0)	1 (5)	0 (0)	4* (21)	

* statistically significant
dr dose related
(a/r) absolute/relative
1 Corrected body weight gain = terminal body weight minus uterine weight minus day 6 body weight.
2 Mean historical control values and ranges of litter incidence (as percentage of total number of litters) for visceral variations: total visceral variations (22; 0-38), dilated renal pelvis (21; 0-38). 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.
3 Mean historical control values and ranges of litter incidence (as percentage of total number of litters) for skeletal variations: misshapen sternebrae (67; 25-92), unossified sternebrae (30; 17-46); incomplete ossification of lumbar arch (1; 0-4).

Transient salivation was observed in mid and high dosed females only for a few minutes after the gavage dose. No salivation was seen when treatment had ceased. Food consumption was dose relatedly decreased in the mid and high dose group, in particularly during GD 6-13. At initiation of treatment (day 6-8) a lower weight gain of dams was observed in the low dose group, but loss of weight was observed in the mid (-1 g) and high dose (-8 g) groups. However, only in the high dose group significantly lower maternal bodyweights were observed up to the end of the study. The corrected body weight gain calculated for the entire exposure period was dose relatedly decreased in the mid and high dose groups (23 and 39% below the control, respectively). Blood parameters showed increased values for MCHC, platelet counts, calcium and triglycerides and decreased values for MCV, Na and Cl in the high dose dams. In the mid dose dams increased values for MCHC and triglycerides were observed. Decreased values were also found for bilirubin in mid and high dose dams. However, according to the study authors turbid lipid serum samples strongly interfere the method of bilirubin analysis and thus the decreases are not considered test substance related. Absolute and relative liver weights were increased in the high dose group (11 and 17% respectively above control values).

There were no effects on gestational parameters. Effects on the foetuses were only observed in the high dose group. In this group the mean foetal body weights were slightly lower and there were slight but statistically significant increases in the litter incidences of some soft tissue and/or skeletal variations. In the mid-dose group a statistically significant increase in litter incidence of total visceral variations and dilated renal pelvis were observed. However these effects were not dose-dependent, not statistically significant at the high dose and within the range of the historical control data. Therefore the visceral variations are not considered compound related.

At the high dose statistically significant increased litter incidences of misshapen sternebrae, unossified sternebra and incomplete ossification of lumbar arch were found. Since these incidences were also at the upper end of, or outside the historical control range they are considered treatment-related.

The NOAEL of dodemorph acetate for maternal toxicity is 30 mg/kg bw per day(equivalent to dodemorph: 25 mg/kg bw/day), based on reduced food consumption, signs of salivation and increased blood values in dams of the 100 mg/kg bw/day dose group. Overt maternal toxicity was observed in the high dose group (300 mg/kg bw per day) which was substantiated by transient

salivation, reduced food consumption, impairments in body weight and bw gain, slight changes in serum electrolytes, increased number of platelets and a marked increase in triglycerides and increased liver weights.

The NOAEL of dodemorph acetate for embryo/foetotoxicity is 100 mg/kg bw (equivalent to dodemorph: 82 mg/kg bw/day), based on a slight decrease in foetal body weights and slight but significant increases in a few skeletal variations (delayed or incomplete ossification process of sternebra and lumbar arch, and increased incidences of misshapen sternebrae) in the high dose group. There were no indications for teratogenicity.

In another (range finding) developmental toxicity study (no GLP, no guideline), dodemorph acetate (purity 98.7%) was administered by gavage to rabbits at dose levels of 200, 600 and 900 mg/kg bw per day on 4 does per group, exposed during days 7-19 of gestation and sacrificed on day 20. Controls were treated with vehicle (olive oil). Body weight and food consumption were recorded and the dams were examined daily for clinical signs of toxicity. Blood samples were taken before sacrifice and examined for haematological parameters and clinical chemistry parameters. Apart from uterus and ovaries also liver and kidneys were removed. On gestation day 20 does were sacrificed and examined macroscopically. Foetuses were removed, weighed, sexed, and observed for gross malformations.

Severe toxicity was observed in the high dose group: drastically reduced or no food consumption, massive body weight loss during treatment; 2 dams died intercurrently, 1 doe was sacrificed in moribund state and one doe died after gavage error. All does showed poor general state, some of them blood in bedding, fur smeared with urine, diarrhoea and/or no defecation. Decrease in WBC RBC, Pt and Ht was noted and a prolonged clotting time was observed. Further, increased plasma AST, ALT, GGT activity as well as increased urea, creatinine, bilirubin, cholesterol and triglyceride levels were recorded. Three does showed ulcerations of the stomach mucosa. Absolute and relative liver and kidney weights were markedly increased. In this group 100% post implantation loss was recorded.

The same, but less severe findings in body weight, food consumption, clinical signs of toxicity, haematology, clinical chemistry and organ weights were also noted in the mid dose group. One doe of this dose group died in poor general condition, all 4 dams had ulcerations in the stomach and also 100% post implantation loss was recorded.
In the low dose group body weight and food consumption were reduced, ALT, GGT, and cholesterol were increased, and an increased post implantation loss (57.5%) was observed, especially due to a high number of late resorptions in 2 does which had no viable foetuses. Foetal toxicity was shown by reduced placental and foetal body weights. Anasarca was observed in 4 and open eye in 7 out of 16 foetuses from a single litter at 200 mg/kg bw. These malformations were considered questionable effects due to the premature status of the foetuses (removed from the uterus on day 20 of gestation instead of day 29).
Dodemorph acetate induces mortality, severe maternal toxicity and post implantation losses at 900 and 600 mg/kg bw per day. At 200 mg/kg bw per day, maternal toxicity and embryo/foetotoxicity (teratogenicity) were also observed.

In a third developmental toxicity study, according to former OECD guideline 414, groups of 15 inseminated rabbits were given dodemorph acetate (purity 92.6%) at a dose of 10, 40 or 120 mg/kg bw per day by gavage on days 7 through 19 of gestation. Controls were treated with vehicle (olive oil). Body weight and food consumption were recorded and the dams were examined daily for clinical signs of toxicity. On gestation day 29 does were sacrificed and examined macroscopically. Foetuses were removed, weighed, sexed, and observed for gross malformations, then preserved for examination of soft tissue and/or skeletal abnormalities.

Table 25 Results from a developmental toxicity study in rabbits

	Dose (mg/kg bw per day)	0	10	40	120	dr
Maternal effects	Mortality	no mortality				
	Clinical signs	no clinical signs of toxicity				
	Pregnant animals	15	13	15	14	
	body weight/weight gain	no toxicologically relevant effects				
	Corrected body weight gain (g)[1]	no toxicologically relevant effects				
	Food consumption	no toxicologically relevant effects				
	Abortions	no abortions				
	Gravid uterine weight (g)	369	366	370	306	
	Corpora lutea	no toxicologically relevant effects				
	Pathology	no toxicologically relevant effects				
Litter response	Live foetuses	no toxicologically relevant effects				
	Foetal weight	no toxicologically relevant effects				
	Pre implantation loss	no toxicologically relevant effects				
	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	0.2	0.3	0.2	0.7	
Foetus examination	No. of foetuses	no toxicologically relevant effects				
	No. of dead foetuses	no toxicologically relevant effects				
	Sex ratio (f/m)	no toxicologically relevant effects				
	Malformations					
	a] external - cleft palate (no. of foetuses) - open eye (no. of foetuses)	 0 0	 0 0	 0 0	 1 4	
	b] soft tissue	no toxicologically relevant effects				
	c] skeletal	no toxicologically relevant effects				
	Variations/retardations	no toxicologically relevant effects				
	a] external	no toxicologically relevant effects				
	b] soft tissue	no toxicologically relevant effects				
	c] skeletal - sternebra irregular shape (foetuses/litter)	1.6	5.0	6.0	10.9*	

* statistically significant
dr dose related
(a/r) absolute/relative
1 Corrected body weight gain = terminal body weight minus uterine weight minus day 7 body weight.

No mortality was recorded during the study, food consumption was not affected and no statistically significant differences were observed for body weight and body weight gain. There were no clinical signs of toxicity and no abnormal findings were recorded at necropsy. The mean gravid uterus weight of the high dose group was clearly but not significantly reduced and reached only about 83% of the control value. Post implantation loss value and early resorptions were increased at high dose, predominantly caused by one doe, which had no viable foetuses at necropsy, but only early resorptions. This doe also showed a slight, not significant increase in post implantation loss. Since similar but more pronounced effects were seen in the preceding preliminary range finding study at higher dose levels (200, 600 and 900 mg/kg bw per day, see above), the increase in early resorptions and post implantation loss is considered substance related.

In the high dose group there were 4 foetuses all from one doe with external malformations, while none were found in the other groups. All 4 foetuses showed open eye; one foetus had in addition cleft palate. The findings were not statistically significant. Because the open eye malformation was also seen in the range finding study in 7 out of 16 foetuses, also from 1 single litter at 200 mg/kg bw per day, it was considered that it was a treatment related malformation. The only skeletal retardation found was an increased incidence for sternebrae with irregular shape (number of affected foetuses per litter) in the high dose group. No effects on does, gestational parameters, or foetuses were observed in the mid and low dose group.

No maternal toxicity was observed. The decrease in mean gravid uterus weight is considered to be the consequence of an increased resorption rate and higher post implantation loss value, and thus a consequence of fetotoxicity rather than maternal toxicity. Thus the NOAEL of dodemorph acetate for maternal toxicity is 120 mg/kg bw/day (equivalent to dodemorph: 98 mg/kg bw/day), i.e. the highest dose tested.
The NOAEL for fetotoxicity is 40 mg/kg bw/day (equivalent to dodemorph: 98 mg/kg bw/day). This was predominantly based on the finding of a slight increase in incidence of a specific malformation (open eye, only in one litter) at the high dose level (120 mg/kg bw per day), a malformation that was also observed in the range finding study at a higher dose level. In addition, at this dose level the percentage of animals with irregularly shaped sternebrae was increased.

4.10.2.2 Human information

No information available

4.10.3 Other relevant information

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4.10.4 Summary and discussion of reproductive toxicity

No data are available for dodemorph. However, the data of the oral reproductive toxicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water.

In a range-finding one-generation reproductive toxicity test in rats with dodemorph acetate litter size and viability and pup weight (day 1) were decreased at a maternal dose of 238 mg/kg bw. However, at this dose also maternal toxicity was observed (decreased body weight and food consumption, altered plasma creatinin and cholesterol). In a 2-generation reproduction toxicity study, maternal toxicity was observed at the top dose (194 mg/kg bw/day). Effects on fertility were not found in these studies. However, both in F1 as in F2 pups of the 2 generation study, fetal body weight was reduced at doses of 64 mg/kg bw and higher. In addition, in one of the 2 groups of F1 pups, pinna unfolding was decreased at 64 mg/kg bw (also observed at both generations in the top dose groups).

In a rat developmental study with doses from 30-300 mg dodemorph acetate/kg bw, no developmental effects were observed at the highest dose that did not induce maternal toxicity (30 mg/kg bw/day). In a developmental study in the rabbit, no maternal toxicity was observed. The NOAEL for maternal toxicity was 120 mg/kg bw/day, i.e. the highest dose tested. (In the repeated dose toxicity studies, only a slight increase in relative liver weight was observed at 80 mg/kg bw 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).
In the fetuses in this study, a slight increase in incidence of malformations (open eye, only in one litter) at the high dose level (120 mg/kg bw per day) was observed, and the percentage of animals with irregularly shaped sternebrae was increased. Although the open eye was observed only in one litter, open eye was also observed in one litter in the range-finding study in the rabbit at a higher dose level, indicating the effect is dose-related. The NOAEL for fetotoxicity was 40 mg/kg bw per day. No historical control data were provided on the incidence of open eye. It is therefore difficult to say whether these effects are substance related or not.

4.10.5 Comparison with criteria

No data are available for dodemorph.

According to the criteria of DSD, substances should be classified as toxic to reproduction category 2 when there are clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or clear evidence in animal studies of impaired fertility in the absence of toxic effects.
Substances should be classified as toxic to reproduction category 3 when there are results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, but where the evidence is insufficient to place the substance in Category 2, or results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, but where the evidence is insufficient to place the substance in Category 2.

According to the criteria of CLP, substances should be classified as Category 1B when there is clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects.
Substances should be classified as Category 2 when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1.

No effects on fertility were found in a 1 generation and 2 generation study with dodemorph acetate. Therefore, dodemorph acetate does not need to be classified for fertility.

In the 2 generation study, reduced body weight gain of the pups was observed at a dose without maternal toxicity (in F1a and F2 pups, but not F1b), as well as decreased pinna unfolding in 1 generation. In addition, in a developmental study with rabbits, an increase in early resoptions and post implantation loss and in four foetuses from one litter an increase in incidence of open eye was observed at the top dose tested (no maternal toxicity). Since these effects are not consistently shown, the effects are considered not severe enough to place the substance in Category 2 of DSD or Category 1B of CLP.

Thus, according to DSD, dodemorph acetate fulfills the criteria to be classified as toxic to reproduction category 3 and assigned the risk phrase R63 (“Possible risk of harm to the unborn child”).

According to CLP, dodemorph acetate fulfills the criteria to be classified as Category 2 reproductive toxicant (H361d).

4.10.6 Conclusions on classification and labelling

No data are available for dodemorph. The data of the oral reproductive toxicity studies with dodemorph acetate can be used for read across to dodemorph, since dodemorph acetate readily dissociates in dodemorph and acetate in water. Therefore, dodemorph should be classified as toxic to reproduction category 3 and assigned the risk phrase R63 (“Possible risk of harm to the unborn child”) according to the criteria of DSD and Category 2 reproductive toxicant (H361d) according to the criteria of CLP.

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 as % change from control -premating during gestation during lactation	N/A	N/A	 -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) -lactation (F1a)	N/A	N/A	0	0 +4 -4	+1	0 +4 -4	-6	-10* -7* -14*
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	92.7	92.3	96.9	73.3*
	auditory canal opening	99.5	100	97.6	73.5*
	eye opening	93.8	97.4	97.2	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.

4.11 Other effects

4.11.1 Non-human information

4.11.1.1 Neurotoxicity

4.11.1.2 Immunotoxicity

4.11.1.3 Specific investigations: other studies

4.11.1.4 Human information

4.11.2 Summary and discussion

4.11.3 Comparison with criteria

4.11.4 Conclusions on classification and labelling

5 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental hazard properties assessment for dodemorph is based on the Draft assessment report (DAR), volume 3 annex B9, prepared in the context of the possible inclusion of dodemorph in Annex I of Council Directive 91/414/EEC (January 2007), RMS The Netherlands).

All tables in the present assessment are copied from the DAR. The tables are renumbered in accordance with the paragraph numbers.

General remark: Most of the studies are performed with dodemorph acetate but these in view of the rapid hydrolysis are applicable to dodemorph.

5.1 Degradation

Table 26: Summary of relevant information on degradation

Method	Results	Remarks

Hydrolysis with ^{14}C-dodemorph acetate Hydrolysis with ^{14}C-dodemorph acetate	DT50 > 32 days at pH 5,7 and 9 at 24-25 ºC. DT50 > 5 days at pH 4, 7, and 9 at 22 ºC.	Guideline study EPA 161-1, radio-labelled substance, acceptable. Guideline study OECD 111, radio-labelled substance, acceptable.
Photolysis with ^{14}C dodemorph acetate	DT_{50} of 3.6 and 1.6 days at pH 7 and 9, respectively	Guideline study EPA 161-2, radio-labelled substance, acceptable.
Aerobic water-sediment system (two systems)	DT_{50} sediment 126 and 281 days, DT_{50} system 53 days	Guideline study directive 95/36/EC,CTB G2.1 (1995), SETAC (1995). Water and sediment were analysed, Radio-labelled substance. acceptable.

It should be noted that in aqueous solution dodemorph acetate dissociates rapidly into dodemorph free base and acetate. As acetate is not relevant for the environmental compartment, it has no toxicological effects, the observed effects can be attributed to dodemorph. Analysis of dodemorph acetate in aqueous solution represents dodemorph instead of dodemorph acetate. Therefore, the study results are for dodemorph.

5.1.1 Stability

Stability in water.

A hydrolysis study with ^{14}C-dodemorph acetate was performed in aqueous buffered and sterilised solutions at pH 5, 7 and 9. The two peaks, which were observed in the chromatograms represent dodemorph (cis and trans) and not dodemorph acetate. It was concluded that in aqueous solution dodemorph acetate dissociates very rapidly into dodemorph free base and acetate whereas dodemorph has been found to be hydrolytically stable at pH 5, 7, and 9 at 24-25 °C (DT50 > 32 days).

In a second study performed with ^{14}C-dodemorph acetate, according to OECD 111 guideline, in sterilised buffered solutions at pH 4, 7, and 9. DT 50 values of > 5 were determined at 22 ºC for pH 4, 7, and 9.

Dodemorph acetate dissociates in dodemorph and acetate. DT50 values are not available, but the process is expected to be fast.

Photolysis in water

Dodemorph is photolysed rapidly in aqueous solutions, the $DT_{50,photolysis}$ was equivalent to 3.6 and 1.6 natural sunlight days at pH 7 and 9, respectively. One unknown minor metabolite at a maximum of 6.7% of applied substance was formed.

Dodemorph acetate dissociates in dodemorph and acetate. The formed dodemorph will be photolysed.

5.1.2 Biodegradation

A ready biodegradation study is not available.

The behaviour of dodemorph in two aerobic water-sediment systems (silty clay loam: a lake near Lelystad (OVP) and silt loam: a pool at Leerdam (SW)), performed with ^{14}C-dodemorph, indicates that residues of dodemorph may remain for a long time. Dodemorph dissipated rapidly from the water layer of both water/sediment systems to less than 10% after 2 – 7 days (for OVP and SW, respectively) and further to < 1% after 14 days (OVP) and 68 days (SW). 15.4% (OVP)- 23.2% (SW) of the applied radioactivity was completely mineralised after 103 days of incubation. The decrease of radioactivity in the water layer was in the first place the result of transfer of activity to the sediment layer and in the second place the result of degradation of dodemorph in the water layer. The total radioactivity in the sediment layer of the OVP increased rapidly to 71% after 1 day, increased further to 87% after 28 days and decreased to 77% after 103 days. After day 1, the amount of the extractable residues and the unextractable residues remained fairly constant. The extractable residues were in the range of 45.5% - 67.2% and the unextractable residues in the range of 14.0% - 30.4%. The radioactivity in the sediment layer for the other system (SW) was 38% after 1 day, increasing to 89% after 14 days and decreasing to 67% after 103 days. The amount of extractable and unextractable activity increased steadily to 55% and 34%, respectively after 14 days and then decreased to 39% and 27%, respectively after 103 days.
All dodemorph which was still present at the end of the study was recovered in the sediment with 42.5 % in the OVP system and 29.9 % in the SW system, respectively. At HPLC analysis only in one peak > 5% (maximum of 7.9%) of applied radioactivity was found in both systems, these were the totals of fractions from the water and sediment layer. The identity of the compounds could not be confirmed, but it is assumed to be cis and/or trans-2,6-dimethylmorpholine.

The following DT_{50} values were determined:

System	**Water DT_{50} [d]**	**Sediment DT_{50} [d]**	**System DT_{50} [d]**
OVP	0.5	281	Value not reliable.
SW	1.5	126	53

5.1.3 Summary and discussion of degradation

Dodemorph is hydrolytically stable, DT50 values >32 days were calculated. Dodemorph is photolysed rapidly in an aqueous solution.

Dodemorph is not rapidly degradable. In water-sediment systems, it dissipates rapidly from water but has long half-lives (>53 days) in the total system. Dodemorph is susceptible to primary degradation but mineralization is slow (15.4% and 23.2% after 103 days).

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Not relevant for this type of dossier.

5.2.2 Volatilisation

Not relevant for this type of dossier.

5.2.3 Distribution modelling

No data available

5.3 Aquatic Bioaccumulation

Table 27: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks
Fish bioaccumulation study	BCF: 583 – 746 L/kg	Dodemorph acetate spiked with radiolabelled dodemorph, flow-through study, OECD 305 guideline, acceptable

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The bioconcentration factor (BCF) of fish (rainbow trout) exposed to dodemorph acetated spiked with radiolabelled dodemorph was determined in a flow-through study. Two concentrations (3 and 30 µg dodemorph acetate/L) were used. Concentrations in water were analysed daily. Edible and non-edible tissue were extracted and analysed for dodemorph. A depuration phase was included in the study. Equilibrium was reached within 2 days. A kinetic BCF as well as BCF based on the ratio of the concentration in the fish and in the water at apparent steady state were calculated for both concentrations. The resulting BCF kinetics values were 746 and 649L/kg wwt for the lower and higher test concentration, respectively. The BCF values for the steady state concentrations were 692 and 583 L/kg wwt for the lower and higher test concentrations, respectively. The lipid content of the fishes was not reported and therefore the BCF values can not be normalised to 5% lipid content.

5.3.2 Summary and discussion of aquatic bioaccumulation

BCF values determined for dodemorph in fish varied between 580 - 750 L/kg.

5.4 Aquatic toxicity

All available studies on the ecotoxicity of dodemorph have been performed with dodemorph acetate. As already mentioned, dodemorph acetate dissociates rapidly in aqueous solutions into acetate and dodemorph. From the HPLC analysis of the applied dodemorph acetate in the aquatic toxicity studies it is clear that the peak in the HPLC analysis represents dodemorph and not dodemorph acetate. For the purpose of classification and labelling, the results from the available studies have been converted to the concentrations of dodemorph using a conversion factor of 0.82 (=281.5 (MW dodemorph)/341.5 (MW dodemorph acetate)), assuming that the bioavailability for dodemorph is the same as for dodemorph acetate.

Table 28: Summary of relevant information on aquatic toxicity
This table shows the lowest available toxicity values for the three aquatic trophic levels fish, invertebrates and algae.

Method	Criteria	Results as mg/l dodemorph acetate	Results as mg/l dodemorph	Test condition and reliability
Acute fish *Oncorhynchus mykiss*	LC_{50}	1.49 – 3.22	1.23 – 2.65	OECD 203 guideline, measured concentrations, acceptable
Chronic Fish *Oncorhynchus mykiss*	NOEC growth and survival	0.12	0.10	OECD revised version of 1997 guideline, measured concentrations, acceptable.
Acute invertebrate *Daphnia magna*	EC_{50}	1.8	1.48	OECD 202 guideline study. Measured concentrations, acceptable.
Chronic invertebrate *Daphnia magna*	NOEC	0.10	0.08	OECD 202 and 211 guideline study, measured concentrations, acceptable.
Algae *Pseudokirchneriella subcapitata*	E_rC_{50} NOE_rC	1.1 0.059	0.91 0.05	OECD 201 guideline study, measured concentrations, acceptable

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

An acute toxicity study with technical dodemorph acetate (purity 93%) was performed with rainbow trout under static conditions according to OECD guideline 203. Five test concentrations were used (range: 1.0 – 10.0 mg dodemorph acetate/L). Test concentrations were analytically monitored. The measured concentrations at the start were approximately 50% of nominal and decreased during the test to 17 – 25% of nominal. Mortality was 100% in the highest test concentration after 72 hours. No mortality was observed in the control and the lower concentrations during the study. The dose-response curve was very steep and LC50 value was considered to lie between 1.49 and 3.22 mg dodemorph acetate/L corresponding to 1.23 and 2.65 mg dodemorph/L), based on mean measured concentrations.

5.4.1.2 Long-term toxicity to fish

The survival and growth of rainbow trout was determined in a 28-days flow-through test according to OECD guideline (revised version of 1997). Five test concentrations were used (0.054 – 1.08 mg dodemorph acetate/L, a control and a solvent control (acetone). Test concentrations were analytically monitored. The mean measured concentrations were between 87 and 138% of the nominal concentrations and analysis of the stock solution showed actual recoveries from 108 to 121%. The mean measured test concentrations ranged from 0.057 – 0.938 mg dodemorph acetate/L. No mortalities occurred, and only two fish in the highest test concentration showed abnormal swimming behaviour. The body lengths of the fish in the three highest test concentrations were significantly reduced compared to control. NOEC was 0.12 mg dodemorph acatete/L corresponding to 0.10 mg dodemorph/L based on the growth of the fish and measured concentrations.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Daphnia magna were exposed to dodemorph acetate (purity of 93%) for 48 hours under static conditions according to OECD guideline 202. Five concentrations were tested (1 – 10 mg dodemorph acetate). Test concentrations were analytically monitored. Mean recovery varied from 34% to 44% of nominal. Immobilisation of 60% and 100% was observed at the two highest test concentration. A steep dose response curve was observed just like in the acute fish study. The EC50 was 1.8 mg dodemorph acetate/L corresponding to 1.48 mg dodemorph/L, based on mean measured test concentrations.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Effects of dodemorph acetate (purity 93%) on mobility and reproduction of *Daphnia magna* were determined under semi-static conditions for 21 days according to OECD guideline 202 and 211. Five test concentrations were used (0.054 – 1.08 mg dodemorph acetate/L). The test water was renewed every 48 hours. Fresh and old test waters were analytically monitored. Measured concentrations were all >80% of nominal (range 81% to 96%). Adult mortality increased with increasing concentrations. Reproduction and body length were significantly reduced in the highest treatment. NOEC values were estimated to be 0.10 mg dodemorph acetate/L for survival and body length, 0.45 mg dodemorph acetate/L for reproduction. The overall NOEC was determined to be 0.10 mg dodemorph acetate/L corresponding to 0.08 mg dodemorph/L, based on nominal concentrations.

5.4.3 Algae and aquatic plants

In the available algae study, green algae were exposed to dodemorph acetate (purity 93%) for 72 hours under static conditions according to OECD guideline 201. Seven concentrations were tested (range: 0.10 – 10 mg dodemorph acetate/L). Concentration series without algae were included. Test concentrations were sampled and analysed at the start and end of the study. Test concentrations at the start were approximately 50% of nominal and decreased to less than 25% after 72 hours of exposure. Mean measured test concentrations varied between 14% and 36% (36% in the highest test concentration). In the highest test concentration without algae mean measured concentration was 43% of nominal. Inhibition of growth and reduced biomass were statistically significant in the four highest concentrations (at nominal 1.0 mg/L and higher). An E_rC_{50} of 1.1 mg dodemorph acetate/L corresponding to 0.91 mg dodemorph/L, and a NOE_rC of 0.059 mg dodemorph acetate/L

corresponding to 0.05 mg dodemorph/L were derived. All values are based on mean measured concentrations.

The test substance concentrations decreased significantly during the study. Nevertheless, the study is considered useful since the results are based on mean measured concentrations. Furthermore, flow-through or semi-static studies in which test substance concentrations may be more stable are very difficult to carry out for algae.

5.4.4 Other aquatic organisms (including sediment)

No data available.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

CLP- Acute aquatic hazards

According to the criteria of the CLP Regulation, a substance is classified for aquatic acute toxicity if in an aquatic acute toxicity study, an $L(E)C_{50}$ of ≤ 1 mg/l is obtained for any of the three trophic levels fish, invertebrates and algae/aquatic plants.

The lowest available L(E)C50 value for dodemorph is 0.91 mg/l obtained in algae. Based on this value, dodemorph fulfils the criteria for classification as Aquatic Acute Cat 1.

Based on the L(E)C50 value of 0.91 mg/l, an acute M-factor of 1 is proposed (0.1 mg/l < L(E)C50 ≤ 1 mg/l).

CLP - Aquatic chronic hazards

According to the criteria of the 2nd ATP to the CLP Regulation the assignment of a hazard category depends on the NOEC value and whether the substance is rapidly degradable or not.

Dodemorph is considered not rapidly degradable (see section 5.1.3). NOEC values for dodemorph are available for all trophic levels. A NOErC of 0.05 mg/l, 0.08 mg/l and 0.10 mg/l were obtained in algae, *Daphnia* and fish, respectively. Dodemorph therefore fulfils criteria for classification as Aquatic Chronic Cat.1.

An M-factor of 1 for chronic toxicity is proposed based on NOEC values 0.01 < NOEC ≤ 0.1 mg/l and the fact that dodemorph is not rapidly degradable.

Directive 67/548/EEC

According to the criteria of Directive 67/548/EEC, a substance can be classified for acute or chronic hazards to the environment. If a substance has acute aquatic toxicity of <100 mg/l and is not readily degradable or has a log Kow of ≥3, it is classified for long-term hazards to the environment. Assignment into division depends on the lowest acute aquatic toxicity value.

The lowest acute aquatic toxicity values for dodemorph is 0.91 mg/l in algae. Dodemorph is not readily degradable (see section 5.1.3). Furthermore, the log Kow value of dodemorph is 4.6. Dodemorph therefore fulfils the criteria for classification with N; R50/53.

Based on the lowest L(E)C50 value of 0.91 mg/l, no specific concentration limits are proposed.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Table 29: Classification according to DSD with SCL and CLP with M-factor.

Substance	Directive 67/548/EEC		CLP Regulation	
	Classification	SCL	Classification	M factor
Dodemorph	N; R50/53		Aquatic Acute category 1 H400: very toxic to aquatic life Aquatic Chronic category 1. H410: very toxic to aquatic life with long lasting effects.	1

RAC evaluation of environmental hazards

Summary of 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%

1

Bibliographic 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

OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of dodemorph according to Directive 91/414/EEC. The summaries included in this proposal are partly copied from the DAR volume 3, annex B. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR Volume 3 and its addendum.

6 REFERENCES

European Commission. Draft Assessment Report dodemorph, prepared by The Netherlands January 2007.

European Commission. Draft Assessment Report dodemorph addendum, prepared by The Netherlands July 2008.

7 ANNEXES

[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.