Committee for Risk Assessment

RAC

Annex 1

Background document

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

bis(α,α-dimethylbenzyl) peroxide

EC Number: 201-279-3
CAS Number: 80-43-3

CLH-O-0000001412-86-217/F

Adopted

8 June 2018

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

8 June 2018

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Bis(α,α-dimethylbenzyl) peroxide

EC Number: **201-279-3**

CAS Number: **80-43-3**

Index Number: **617-006-00-X**

Contact details for dossier submitter:

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Version number: 1.0 **Date: 27.04.2017**

Note on confidential information

Please be aware that this report is intended to be made publicly available. Therefore it should not contain any confidential information. Such information should be provided in a separate confidential Annex to this report, clearly marked as such.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON BIS(α,α-DIMETHYLBENZYL) PEROXIDE

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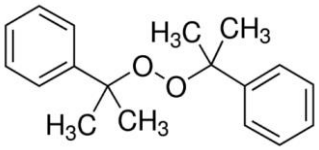
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Bis(α,α-dimethylbenzyl) peroxide 1,1'-(dioxydipropane-2,2-diyl)dibenzene
Other names (usual name, trade name, abbreviation)	Dicumyl peroxide Cumene peroxide Diisopropylbenzene peroxide Perkadox BC-FF
ISO common name (if available and appropriate)	
EC number (if available and appropriate)	201-279-3
EC name (if available and appropriate)	Bis(α,α-dimethylbenzyl) peroxide
CAS number (if available)	80-43-3
Other identity code (if available)	Index number in Annex VI of the CLP Regulation: 617-006-00-X
Molecular formula	C18H22O2
Structural formula	
SMILES notation (if available)	O(OC(c1ccccc1)(C)C)C(c2ccccc2)(C)C
Molecular weight or molecular weight range	270.37 Da
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	
Description of the manufacturing process and identity of the source (for UVCB substances only)	
Degree of purity (%) (if relevant for the entry in Annex VI)	

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Bis(α,α-dimethylbenzyl) peroxide	**> 99%**	Org. Perox. F H242 Skin Irrit. 2 H315 Eye Irrit. 2 H319 Aquatic Chronic 2 H411	10 joint entries with a total of 870 notifiers have self-classified with the same classification as the harmonised classification. 1 notifier has classified with these: Org. Perox. E Aquatic Acute 1

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	617-006-00-X	1/C18H22O2/c1-17(2,15-11-7-5-8-12-15)19-20-18(3,4)16-13-9-6-10-14-16/h5-14H,1-4H3	201-279-3	80-43-3	Org. Perox. F Skin Irrit. 2 Eye Irrit. 2 Aquatic Chronic 2	H242 H315 H319 H411	GHS02 GHS07 GHS09	H242 H315 H319 H411			
Dossier submitters proposal	617-006-00-X	1/C18H22O2/c1-17(2,15-11-7-5-8-12-15)19-20-18(3,4)16-13-9-6-10-14-16/h5-14H,1-4H3	201-279-3	80-43-3	**Add** **Repr 2** **Remove** **Skin Irrit. 2** **Eye Irrit. 2**	Add H361d Remove H315 H319	Add GHS08 Remove GHS 07	Add H361d Remove H315 H319			
Resulting Annex VI entry if agreed by RAC and COM	617-006-00-X	1/C18H22O2/c1-17(2,15-11-7-5-8-12-15)19-20-18(3,4)16-13-9-6-10-14-16/h5-14H,1-4H3	201-279-3	80-43-3	Org. Perox. F Repr. 2 Aquatic Chronic 2	H242 H361d H411	GHS02 GHS08 GHS09	H242 H361d H411			

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*hazard class not assessed in this dossier*	No
Oxidising gases	*hazard class not assessed in this dossier*	No
Gases under pressure	*hazard class not assessed in this dossier*	No
Flammable liquids	*hazard class not assessed in this dossier*	No
Flammable solids	*hazard class not assessed in this dossier*	No
Self-reactive substances	*hazard class not assessed in this dossier*	No
Pyrophoric liquids	*hazard class not assessed in this dossier*	No
Pyrophoric solids	*hazard class not assessed in this dossier*	No
Self-heating substances	*hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*hazard class not assessed in this dossier*	No
Oxidising liquids	*hazard class not assessed in this dossier*	No
Oxidising solids	*hazard class not assessed in this dossier*	No
Organic peroxides	*hazard class not assessed in this dossier*	No
Corrosive to metals	*hazard class not assessed in this dossier*	No
Acute toxicity via oral route	*hazard class not assessed in this dossier*	No
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	*hazard class not assessed in this dossier*	No
Skin corrosion/irritation	**Proposal to delete classification**	**Yes**
Serious eye damage/eye irritation	**Proposal to delete classification**	**Yes**
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	*hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*hazard class not assessed in this dossier*	No
Carcinogenicity	*hazard class not assessed in this dossier*	No
Reproductive toxicity	**harmonised classification proposed**	**Yes**
Specific target organ toxicity-single exposure	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The previous classification dates from before the CLP regulation (CLP00). It has not been possible to find out what the basis for this classification is.

RAC general comment
The current proposal for harmonised classification for bis(α,α-dimethylbenzyl) peroxide is intended to cover new data on developmental toxicity that has become available. However, in the process of evaluating the substance it was discovered that the current harmonised classifications for skin and eye irritation were not supported by the available data in the current REACH registration dossier. These classifications date back to before the CLP Regulation came into force and the grounds at that time, for giving this substance a harmonised classification as an irritant, have not been found. Although skin and eye irritation are not prioritised endpoints, while proposing a classification for reproduction toxicity, the dossier submitter (DS) proposed to remove the former classifications at the same time.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Change in existing entry due to new data

Further detail on need of action at Community level

The main reason to propose a harmonised classification for bis (α,α-dimethylbenzyl) peroxide is new data on developmental toxicity. However, in the process of evaluating the substance it was discovered that the current harmonised classifications for skin and eye irritation are not supported by data in the registration. These classifications date back to before the CLP regulation and the grounds for giving this substance a harmonised classification as an irritant at that time have not been found. Peroxides are however known to have irritant potential and thus the classification was possibly given due to the fact that the test substance is a peroxide. The studies on skin and eye irritation in the registration do not seem to support or confirm the current classifications. Although skin and eye irritation are not prioritised endpoints the dossier submitter proposes to consider removing the classifications for skin and eye irritation in the same process as considering a classification for reproduction toxicity.

5 IDENTIFIED USES

Dicumyl peroxide is used in the following products: polymers. It is used in formulation of mixtures and/or re-packaging and is for the manufacture of plastic products, rubber products and chemicals.

Release to the environment is likely to occur from industrial use: formulation in materials, formulation of mixtures and as processing aid. Other release to the environment is likely to occur from outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment).

Dicumyl peroxide can be found in products with material based on plastic (e.g. food packaging and storage, toys, mobile phones), wood (e.g. floors, furniture, toys) and stone, plaster, cement, glass or ceramic (e.g. dishes, pots/pans, food storage containers, construction and isolation material).

6 DATA SOURCES

REACH registration, ECHA dissemination site

Full study reports for:

- Acute dermal irritation study in rabbits, LSR Report no 92/0905
- Acute eye irritation study in rabbits, LPT Report no 25133
- 90-day repeat dose oral gavage toxicity study in rats, study number 788.361.4506
- Prenatal developmental toxicity study in rats by oral administration, study no. 788.410.4505

Systematic literature search and relevant studies found.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	White, granular solid	Registration	
Melting/freezing point	Melting point, 39,8 °C	Registration	
Boiling point	Data waiving	Registration	
Relative density	1.1 g/cm³ at 17.7 °C	Registration	
Vapour pressure	< 10 Pa at 60 °C, <10 Pa at 70 °C, <10 Pa at 80 °C, 10 Pa at 90 °C, 29 Pa at 100 °C, 71 Pa at 110 °C (interpolation) 146 Pa at 120 °C (interpolation)	Registration	
Surface tension	Data waiving	Registration	
Water solubility	0,43 mg/L	Registration	
Partition coefficient n-octanol/water	Log PoW 5.6 at 25 °C	Registration	
Flash point	130,7 oC at 101,3 kPa	Registration	
Flammability	non flammable	Registration	
Explosive properties	non explosive	Registration	
Self-ignition temperature	Data waiving	Registration	
Oxidising properties	Data waiving	Registration	
Granulometry	1700 µm (Mass median diameter)	Registration	

Stability in organic solvents and identity of relevant degradation products	Dicumyl peroxide is reported to be stable in toluene for 1 week in a refrigerator (Reliability 4 (not assignable))	Registration	
Dissociation constant	Data waiving	Registration	
Viscosity	Data waiving	Registration	

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated for this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated for this dossier.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not evaluated for this dossier.

10.2 Acute toxicity - dermal route

Not evaluated for this dossier.

10.3 Acute toxicity - inhalation route

Not evaluated for this dossier.

10.4 Skin corrosion/irritation

Table 9: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results** **-Observations and time point of onset** **-Mean scores/animal** **-Reversibility**	**Reference**
OECD 404, deviation: no vehicle used with the test substance	Rabbit, New Zealand White, male, three animals	Dicumyl peroxide	0,5 g, 4 hours of exposure	Time points at which grading/scoring took place was 1, 24, 48 and 72 hours. The following observations were made: Grade 1 erythema was observed at the test site of two rabbits at 24 hours, and in one rabbit at 48 hours. Grade 1 oedema was seen in one rabbit at 24 hours. No dermal effects were seen at the test site of the remaining rabbit during the 72 hour observation period. Mean score for rabbits at 24, 48 and 72 hours, erythema/oedema: - Initial test: 0/0 - Confirmatory test 1: 0,7/0,3	Life Science Research Limited, 1993.

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
				- Confirmatory test 2: 0,3/0 The effects in both rabbits were reversed at 72 hours. The control sites did not show any response to the control procedure.	

Table 10: Summary table of human data on skin corrosion/irritation

NA

Table 11: Summary table of other studies relevant for skin corrosion/irritation

NA

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

The effects of the test substance on the skin was very slight, only grade one for both erythema and oedema, and was seen in only two out of three rabbits. The mean scores at 24, 48 and 72 hours were below 1 for both effects and in all three rabbits and were reversed at 72 hours.

The study is rather old, but mainly performed according to GLP and OECD guideline 404. There is however one deviation from the guideline: the laboratory has not used a vehicle with the test substance. The test substance is a crystalline powder and it may be that the substance does not show its true irritating potential when applied in a dry form. In the guideline it is stated that one should use the smallest amount of liquid necessary in order to ensure good skin contact.

The substance currently has a harmonised classification for skin irritation. This classification dates back to before the CLP regulation and the grounds for giving it a harmonised classification as an irritant at that time have not been found. Peroxides are however known to have irritant potential, as pointed out in the Guidance on the application of the CLP criteria[1] and thus the classification was possibly given due to the fact that the test substance is a peroxide. This study however does not seem to support or confirm the current classification.

10.4.2 Comparison with the CLP criteria

The relevant CLP criteria state that for a substance to be considered a skin irritant the following criteria must be fulfilled:

(1) Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or

(2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling;

In this study the mean values for erythema/oedema was 0/0 in the initial test (first animal) and 0,7/0,3 in animal no. 2 and 0,3/0 in animal no. 3. Thus the criteria for classifying the substance as a skin irritant are not fulfilled.

[1] Guidance on the Application of the CLP Criteria, Version 4.1 June 2015: 3.2.2.1.2.1. Consideration of physico-chemical properties,

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

In the present study the test substance only has a slight skin irritant effect in rabbits and the effects are reversible at 72 hours after administration of the substance. There is some uncertainty concerning the quality of the study since the laboratory did not use a vehicle in administering the test substance. However, even with this uncertainty it seems plausible that the substance does not have enough irritant effect to fulfil the CLP criteria for skin irritation.

In conclusion there does not seem to be sufficient grounds to keep the current classification as a skin irritant, despite the fact that the study was not completely in accordance with the OECD guideline.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS included a study on New Zealand White rabbits to assess the skin irritation potential of bis(α,α-dimethylbenzyl) peroxide. The study was mainly performed according to GLP and OECD TG 404. There was however one deviation from the guideline: the laboratory had not used a vehicle with the test substance, which was a crystalline powder. It may be that the substance did not show its true irritating potential when applied in dry form, as in the OECD TG 404, it is stated that the smallest amount of liquid necessary in order to ensure good skin contact should be used.

The effects of the test substance on the skin were very slight, grade one for both erythema and oedema, and were seen in only two out of three rabbits. The mean scores at 24, 48 and 72 hours were below one for both effects and in all three rabbits and were reversed at 72 hours, see table 9 on the background document. As the study results were below the classification criteria for skin irritation, the DS proposed to remove the existing classification.

Comments received during public consultation

Four MSCAs supported the DS proposal to remove the existing classification. Two MSCAs noted that no vehicle was used in the study and that the purpose of the vehicle was to optimise the contact between the solid substance and the skin. These two MSCAs considered there was a reasonable possibility of an increased skin reaction if the substance had been applied with a vehicle, and thus they questioned whether this study should be considered sufficiently robust to declassify the substance. One of these MSCAs disagreed with the DS proposal to declassify because in their opinion the study suffered from a serious deficiency.

Assessment and comparison with the classification criteria

RAC agrees that the skin irritation study was deficient since the laboratory did not use a vehicle in administrating the test substance, which is lipophilic with a Log K_{OW} of 5.6 and was administered in a crystalline state, raising doubts as to whether without a vehicle, it was made sufficiently bioavailable in the test.

In addition RAC noted that according to ECHA Guidance on the Application of the CLP

Criteria (which cross refers to ECHA Guidance on Information Requirements & Chemical Safety Assessment, Chapter R7, section R.7.2.6.2 "Testing and assessment strategy for skin corrosion/irritation"), if a substance is a peroxide it can be considered as a skin irritant Cat. 2[2]. Given the uncertainty of the available test data, the mentioned 'evidence to the contrary' is lacking.

RAC recommended not to remove the current classification based on lack of proper data and in conclusion, agreed in line with the guidance to **retain the current classification of Skin Irrit. 2; H315.**

10.5 Serious eye damage/eye irritation

Table 12: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
OECD 405, some lacking information on purity, impurities, no information on anaesthesia, no justification for using non-Albino rabbits.	Rabbits, Himalayan, males, three animals	Dicumyl peroxide	100 mg, the eye was rinsed 1 h after administration, according to guideling	Time points at which grading/scoring took place was 1, 24, 48 and 72 hours. The following effects were seen: - grade 1 opacity in animal 3 at 24 h and 48 h. - grade 1 redness in animals 2 and 3 at 24 h. Mean score for rabbits at 24, 48 and 72 hours, cornea/iris/redness/chemosis: - Animal 1: 0/0/0/0 - Animal 2: 0/0/0.3/0 - Animal 3: 0.7/0/0.3/0 The effects in all rabbits were reversed at 72 hours. The control sites did not show any response to the control procedure.	LPT Laboratory of Pharmacology and Toxicology GmbH, 2010

Table 13: Summary table of human data on serious eye damage/eye irritation

NA

Table 14: Summary table of other studies relevant for serious eye damage/eye irritation

NA

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

There was a small degree of opacity seen in the cornea of the third animal at 24 and 48 hours. Grade 1 opacity is described as "scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible". There was also some redness of the conjunctivae in all three animals at 1 hour

[2] **Figure R.7.2-2 line 1b** Consider classifying as: corrosive (Skin Corrosive Cat. 1B) if the substance is a hydroperoxide, or irritating (Skin Irritant Cat. 2) if the substance is a peroxide **OR** Provide evidence for the contrary.

and in two animals at 24 hours. Grade 1 redness is described as "some blood vessels hyperaemic (injected)". A fluorescein test was performed at 24 hours after administration and revealed corneal staining in animal no. 3 (up to 25 % of the surface). At 72 hours all effects were reversed in all three animals. The untreated eye that served as control did not show any pathological changes. No other effects were reported in the report.

The study is fairly new and seems mostly to be performed according to guideline. There are some deviations however, such as a lack of information on purity, and the presence of impurities. There is also a lack of information on the application of anaesthesia, which is a requirement in the most recent guideline. This may not have been a requirement at the time of the study however. The laboratory has used Himalayan rabbits, which are not albino. According to the guideline a justification must be given if the albino rabbit is not used. Such a justification is not given in the study report.

The substance currently has a harmonised classification for eye irritation. This classification dates back to before the CLP regulation and the grounds for giving it a harmonised classification as an irritant at that time have not been found. Peroxides are however known to have irritant potential and thus the classification was possibly given due to the fact that the test substance is a peroxide. This study however does not seem to support or confirm the current classification.

10.5.2 Comparison with the CLP criteria

The relevant CLP criteria state that for a substance to be considered an eye irritant the following criteria must be fulfilled:

Irritating to eyes (Category 2) if, when applied to the eye of an animal, a substance produces:
– at least in 2 of 3 tested animals, a positive response of:
– corneal opacity ≥ 1 and/or
– iritis ≥ 1, and/or
– conjunctival redness ≥ 2 and/or
– conjunctival oedema (chemosis) ≥ 2
– calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

In this study the mean score for opacity of the cornea/iritis/redness of the conjuntivae/chemosis of the conjunctivae was 0/0/0/0 for animal 1, 0/0/0.3/0 for animal 2 and 0.7/0/0.3/0 for animal 3. Thus the criteria for classifying the substance as an eye irritant are not fulfilled.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

In the present study the test substance only has a slight eye irritant effect in rabbits and the effects are reversible at 72 hours after administration of the substance. The study seems to be performed mostly according to guideline and seems to be of good quality.

In conclusion there does not seem to be sufficient grounds to keep the current classification as an eye irritant.

RAC evaluation of serious eye damage/irritation
Summary of the Dossier Submitter's proposal The DS included a study on Himalayan rabbits to assess the eye irritation potential of bis(α,α-dimethylbenzyl) peroxide. The study was conducted in 2010 according to OECD TG 405. There were some deviations however, such as a lack of information on the presence of impurities. There was also a lack of information on the application of anaesthesia, which is a requirement in the most recent version of the guideline, but was

to be applied on a case-by-case basis in an earlier version used at the time of the study. The laboratory used Himalayan rabbits, which were not albino rabbits and according to the guideline a justification must be given if the albino rabbit is not used. Such a justification was not given in the study report.

There was a small degree of opacity seen in the cornea of animal no. 3 at 24 and 48 hours. Grade 1 opacity was described as "*scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible*". There was also some redness of the conjunctivae in all three animals at 1 hour and in two animals at 24 hours. Grade 1 redness was described as "*some blood vessels hyperaemic (injected)*". A fluorescein test was performed at 24 hours after administration and revealed corneal staining in animal no. 3 (up to 25 % of the surface). At 72 hours all effects were reversed in all three animals. The untreated eye that served as the control did not show any pathological changes. No other effects were reported in the report, see table 12 in the background document.

As the values from the study results were below those in the classification criteria for eye irritation, the DS proposed to remove the existing classification.

Comments received during public consultation

Four MSCAs supported the DS proposal to remove the existing classification.

Assessment and comparison with the classification criteria

RAC agrees with the DS that the test substance had only a slight eye irritant effect in rabbits and the effects were reversible at 72 hours after administration. However, considering the lipophilicity and the very low water solubility, the effects seen could be related to a physical/mechanical irritation of the particles in the eye. To adequately observe the irritation effects of this lipophilic substance, an appropriate vehicle should have been used.

In conclusion RAC agreed to **retain the current classification as Eye Irrit. 2; H319**.

10.6 Respiratory sensitisation

Not evaluated for this dossier.

10.7 Skin sensitisation

Not evaluated for this dossier.

10.8 Germ cell mutagenicity

Not evaluated for this dossier.

10.9 Carcinogenicity

Not evaluated for this dossier.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Not evaluated for this dossier.

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Not evaluated for this dossier.

10.10.3 Comparison with the CLP criteria

Not evaluated for this dossier.

10.10.4 Adverse effects on development

Table 15: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Developmental toxicity study (OECD guideline 414) Rats: 24 sperm-positive Wistar rats/treatment group Reliability score: 1	Dicumyl peroxide Purity: 99.0% Oral: gavage 0, 50, 150, 450 mg/kg bw/day vehicle: sunflower oil Exposure: Days 5-19 of gestation (daily)	Maternal and developmental NOAEL: 150 mg/kg bw/day Maternal and developmental LOAEL: 450 mg/kg bw/day **Maternal toxicity:** Mortality: **Control, 50 and 150 mg/kg** bw/day dose groups: No mortality **450 mg/kg** bw/day dose group: one dam died on gestation day 20 (the day of scheduled necropsy. Clinical symptoms: **control group**: alopecia in one female **50 mg/kg** bw/day dose group: no clinical symptoms. **150 mg/kg** bw/day dose group: salivation (4/21 dams). **450 mg/kg** bw/day dose group: No clinical signs in 7/17 dams. Salivation (8/17 dams); piloerection (3/17 dams); alopecia (3/17); reduced activity, vaginal bleeding, pale, cold, hypotonicity and red colouration around red eye (deceased dam). Necropsy findings: **0, 50 and 150 mg/kg** bw/day dose groups: no necropsy findings. **450 mg/kg** bw/day dose group: No necropsy findings in 11/17 dams. In the remaining dams: enlarged adrenals (4/17 dams); blood in uterus (3/17); enlarged spleen (2/17); uterus filled up with blood (1/17); stomach distended filled up with darker content (1/17); pale liver and pale kidneys (1/17). See confidential annex for individual data. Food consumption: **50 mg/kg** bw/day dose group: a statistically significant temporary decrease in	Study report 788.410.4505, Toxi-Coop Zrt. (2014) (not published)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		food intake was recorded. **150 and 450 mg/kg** bw/day dose groups: a statistically significant dose related decrease in the food consumption was recorded in the whole treatment period. Body weight: **50 mg/kg** bw/day dose group: a transient decrease in body weight gain. **150 and 450 mg/kg** bw/day dose groups: lower mean body weight, lower corrected body weight, transient weight loss day 5-8 of gestation, and markedly reduced body weight gain and corrected body weight were observed. See annex I and confidential annex for more details. All treatment groups had positive weight gain at the end of treatment period compared with the start weight. **Foetal toxicity:** **50 and 150 mg/kg** bw/day dose groups: no statistically significant effect on the intrauterine development of embryos and foetuses. **450 mg/kg** bw/day dose group: statistically significant increase in the post-implantation loss (17%, 15/17 litters) compared to in the control group (7 %, 14/23 litters). By consequence, the number of viable foetuses in the 450 mg/kg bw/day dose group (9.0/litter) was statistically significantly lower than in the control group (11.6/litter). Furthermore, a statistically significant increase in total intrauterine mortality was observed. The total intrauterine mortality in the high dose group (65 cases) was 29 % of the number of examined corpora lutea, compared to 14% in the control group. Foetal weight: **50 and 150 mg/kg** bw/day dose groups: no statistically significant decrease in the pups body weight compared with control group. **450 mg/kg** bw/day dose group: increase in percentage of foetuses with decreased body weight (11/17 litters; 31 cases) compared with control group (5/11; 6 cases). External malformations: **50 and 150 mg/kg** bw/day dose groups: no external malformations were observed. **450 mg/kg** bw/day dose group: mal-rotated fore- and hindlimbs in six foetuses (5/17 litters; 6 cases; statistically significant) and hydrops fetalis in one foetus. Visceral variations: Hydroureter (bilateral) in 4 pups **50 mg/kg** bw/day dose group: hydroureter (bilateral) in two cases. **150 mg/kg** bw/day dose group: no visceral variations. **450 mg/kg** bw/day dose group: hydroureter (bilateral) in two cases (in two litters). Visceral malformations: four malformations in three pups **control group**: one pup with an absent brain tissue and one with situs intersus	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		totalis **50 mg/kg** bw/day dose group: no visceral malformations. **150 mg/kg** bw/day dose group: one pup with absent lung lobes and with situs intersus totalis. **450 mg/kg** bw/day dose group: no visceral malformations. Skeletal variations: **50 mg/kg** bw/day dose group: incomplete ossified sternum (2 cases; 2/20 litters), incomplete ossification marked of skull bones (2 cases; 2/20 litters), one case of not ossified supraoccipital, thoracic or lumbar centra (3 cases; 3/20 litters) and 7 cases (3/20 litters) of wavy ribs. **150 mg/kg** bw/day dose group: incomplete ossified sternum (8 cases; 5/21 litters), one case incomplete ossification (more than three bones), 4 cases (1/21 litters) of incomplete ossification marked of skull bones, one case of not ossified supraoccipital, thoracic or lumbar centra (2 cases; 2/21 litters) and 16 cases (7/21 litters) of wavy ribs. **450 mg/kg** bw/day dose group: incomplete ossification of skull bones (10 cases; 8/17 litters), incomplete ossified sternum (10 cases; 9/17 litters), metacarpal/metatarsal (4 cases; 4/17 litters), thoracic or lumbar centra (4 cases; 4/17 litters) and wavy (24 cases; 11/17 litters) and marked wavy ribs (6 cases; 5/17 litters). Skeletal malformations: **50 mg/kg** bw/day dose group: no skeletal malformations. **150 mg/kg** bw/day dose group: short and/or bent scapula (3 cases; 2/21 litters). **450 mg/kg** bw/day dose group: short and/or bent scapula (12 cases, 9/17 litters), clavicular (2 cases; 2/17 litters), humerus (9 cases; 7/17 litters), radius (8 cases; 7/11 litters) and ulna (5 cases; 5/17 litters).	

Table 16: Summary table of human data on adverse effects on development

Not relevant for this dossier.

Table 17: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Prenatal developmental toxicity study: Re-evaluation of rat foetal skeletons from Toxi-Coop ZRT study No. 788.410.4505 with dicumyl peroxide (BSL Bioservices)		104 pups (24%) were selected for re-evaluation.	Findings in the original study was confirmed.	BSL Bioservices

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
White leghorn chicken embryos, 3-day old	Dicumyl peroxide, administered in the inner shell membrane of air chamber.	Doses: 0.38, 0.75, 1.5 and 3.0 µmole/egg. Vehicle acetone. 30 eggs/dose. Treatment time was 14 days.	The NOAEC was 0.38 µmole/egg. High frequency of malformations (defects of the right eye and right wing, twisting and stunting of the back, and defects of the coelomic wall).	Korhonen A, Hemminki K, Vainio H, 1984, Environmental research 33, 54-61.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

One developmental toxicity study in rats has been performed with exposure to dicumyl peroxide, and the maternal and foetal toxicity findings are presented in table 15.

Animals treated with dicumyl peroxide exhibited signs of moderat toxicity, including adverse clinical symptoms, some necropsy findings, decreased corrected body weight, weight loss, markedly reduced body weight gain, corrected body weight, and reduced food consumption. These effects were marked in dams of the highest treatment group (450 mg/kg bw/day) and this dose is considered a LOAEL for both maternal and developmental effects.

Mortality, clinical symptoms, necropsy

One dam died at the 450 mg/kg bw/day dose group on gestation day 20 (the day of scheduled necropsy) with the following adverse clinical symptoms: vaginal bleeding, piloerection, paleness, coldness and hypotonicity. However, there are no pathological examination data of the foetuses from the deceased dam – examination of foetuses from deceased dams is usually conducted when the death occurs on the day of scheduled necropsy. The death was considered by the performing laboratory to be treatment related, although it is also stated in the study report that the dam "died due to unclear reason"[3]. Other studies have not shown any mortality at higher dose level (28-day study, 600 mg/kg bw/day) so it is not obvious that the death is treatment related. No mortality was observed in the 50 and 150 mg/kg bw/day dose groups.

No clinical observations were noted for the dams in the 50 mg/kg bw/day dose group. The only clinical sign in the 150 mg/kg bw/day dose group was salivation, seen in four (4/21) dams. Salivation was seen in eight dams (8/17 dams) in the 450 mg/kg bw/day dose group. Salivation was judged to be treatment-related however, it was not considered an adverse effect. In the 450 mg/kg bw/day dose group, 1/17 dams had vaginal bleeding, 3/17 had piloerection and 1/17 was hypotonic. This was considered adverse clinical signs and an effect of the test item. In total 10/17 dams had clinical symptoms and no clinical signs was seen in the remaining 7 dams.

Necropsy findings in the high dose group were: 4/17 dams had enlarged adrenals and bloody uterine content (blood in the uterus (2/17 dams), blood in uterine horn (1/17 dam) and uterus filled with blood (1/17 dam)). One dam had an enlarged spleen. These findings were considered to be treatment related. There were no necropsy findings in the remaining 11/17 dams examined in the high dose group.

Overall, a majority of the examined dams did not have adverse clinical symptoms, and only 4/17 dams (23 %) had both adverse clinical signs and necropsy findings, while 5/17 dams (29 %) had no adverse clinical signs and no necropsy findings. Another 5 dams had salivation and/or alopecia as only clinical signs and no necropsy findings.

Food consumption

[3] Appendix II, full study report

Evaluation of food consumption data shows that there was a test substance treatment related decrease in the average food intake in the 150 and 450 mg/kg bw/day dose groups, and a temporary decrease in the average food intake in the 50 mg/kg bw/day dose group. The food consumption reduction in the 150 mg/kg bw/day dose group, although statistically significant, was judged to be not adverse and biologically non-relevant since the lower food consumption only resulted in a small reduction of body weight (less than 10% lower than control). When the individual food consumption data for the dams in the high dose group was compared with the data for observed clinical signs and its adversity, there was no clear correlation between lower food intake and adverse clinical symptoms. See confidential annex, figure 2, for more details.

Body weight

Evaluation of the body weight (bw) parameters shows a dose-dependent decrease in all recorded bw parameters, for the 150 and 450 mg/kg bw/day dose groups. The decrease in the body weight parameters are considered to be related to the test item. Further, a transient reduced body weight gain was noticed in the 50 mg/kg bw/day dose group and it is considered to be a non-adverse effect. In the 150 mg/kg bw/day group the body weight reduction at the end of treatment was less than 10 % lower than the control, however body weight gain was reduced by 15%. The dams of the high dose group had a body weight at the end of treatment that was 17% lower than the control dams, however the body weigth gain was about half of the gain seen in the control group. At the end of the treatment period, all dams in all treatment groups gained some weight compared with the start weight.

The body weight parameters of the dams with adverse clinical signs did not differ with statistical significance from the dams without such signs (figure 2, confidential annex). Thus, reduction both in food intake and body weight gain alone could not explain the observed clinical signs and necropsy findings.

Toxicity in pups

In the 450 mg/kg bw/day dose group, examination of the dams showed a statistically significant increase in post-implantation loss (17%) compared with the control group (7%). There were 32 cases of post-implantation loss. Ten of these cases occurred in five dams without clinical or necropsy findings.

A statistically significant decrease in the number of viable foetuses was observed in the high dose group and this was considered treatment related. Furthermore, a statistically significant increase in total intrauterine mortality was observed. There were 65 cases of intrauterine mortality. Five dams with no clinical signs or necropsy findings had 20 cases (20/65) of the total intrauterine mortality; i.e., ~1/3 of the total intrauterine mortality was found in dams without any adverse clinical symptoms or necropsy findings.

This suggests that post-implantation loss and increased intrauterine mortality was not related to maternal clinical symptoms nor necropsy findings in the dams and thus raises a concern for the developmental effects of dicumyl peroxide.

Furthermore, there was an increase in the percentage of foetuses with body weight retardation in the 450 mg/kg bw/day dose group (11/17 litters; 31 cases) compared with control group (5/23; 6 cases). These observations could not be explained by maternal toxicity, since several dams without adverse clinical signs, necropsy findings, or drastically reduced body weight or food intake, had foetuses with decreased body weight. There was no difference in the incidence of pups with decreased body weight in the 50 (5/20 litters; 5 cases) and 150 (7/21 litters; 8 cases) mg/kg bw/day dose groups compared with control group (5/23 litters; 6 cases).

External examination of the pups in the 450 mg/kg bw/day dose group showed malrotated fore- and hindlimbs in six foetuses (5/17 litters; 6 cases, statistically significant) and hydrops fetalis in one foetus. This was considered to be treatment related. Of the six cases with malrotated fore- and hindlimbs, none of them were from the 3/17 dams with adverse clinical symptoms, and 3/6 cases were from two dams with no clinical and necropsy findings.

There was a high incidence of foetuses with skeletal malformations in the 450 mg/kg bw/day dose group: short and/or bent scapula (12 cases, 9/17 litters), clavicular (2 cases; 2/17 litters), humerus (9 cases; 7/17 litters), radius (8 cases; 7/11 litters) and ulna (5 cases; 5/17 litters). In the 150 mg/kg bw/day dose group short and/or bent scapula (3 cases; 2/21 litters) were recorded. **This high incidence of malformations,**

without marked maternal toxicity, is sufficient to raise a concern about the developmental effects of dicumyl peroxide.

In the 450 mg/kg bw/day dose group, there was a statistically significant increase in the incidence of skeletal variations such as incomplete ossification of skull bones, incomplete ossified sternum, metacarpal/metatarsal, and wavy and marked wavy ribs, and these incidences occurred without adverse maternal toxicity. Similarly, in the 150 mg/kg bw/day dose group some variations were observedwithout clear correlation to maternal clinical signs.

Maternal toxicity is apparent in the present study, but there is no clear connection between maternal toxicity and foetal malformation, not even in the high dose group. This indicates that the developing foetuses are more sensitive than the dams to exposure to the test substance. The evaluation of the presented data supports the conclusion that the observed developmental effects following the exposure to dicumyl peroxide are not secondary non-specific consequences of maternal toxicity.

Re-evaluation of the foetal skeletons (BSL Bioservices).

On ECHAs dissemination site, the registrant has written "Considering the high incidence of skeletal malformation in the high dose group and some ambiguous effects in the mid-dose group, the study results have been re-evaluated by an external pathologist. The result of the re-examination confirmed that the skeletal findings critical to the result of this study were essentially reliable." This re-evaluation was also available to the dossier submitter. The re-evaluation does indeed confirm the findings in the foetal skeletons, however it was not within the scope of the re-evaluation to evaluate the maternal toxicity nor did they look at the individual data to compare effects in the individual dams and foetuses. In the context of this classification the re-evaluation does not provide any new information.

Non-guideline supporting study:

The registrant has included a non-guideline embryotoxicity study in white leghorn chicken embryos in the registrations. Dicumyl peroxide was administered to three-day old chick embryos in the inner shell membrane of air chamber at the following doses: 0.38, 0.75, 1.5 and 3.0 µmole/egg. 30 eggs/dose. Treatment time was 14 days. This study shows a high frequency of malformations. For more details see annex I.

10.10.6 Comparison with the CLP criteria

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. For dicumyl peroxide findings concern developmental toxicity, which is described in CLP Annex 1: 3.7.1.4. Adverse effects on development of the offspring:

> *Developmental toxicity includes, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.*

Classified substances may be allocated to one of two categories – 1A/B or 2. In the Guidance on the application of CLP criteria the following is stated:

> ***Category Repr. 1A*** *Known human reproductive toxicant: The classification of a substance in Category 1A is largely based on evidence from humans.*
>
> ***Category Repr. 1B*** *Presumed human reproductive toxicant: The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic*

information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Category Repr. 2 *Suspected human reproductive toxicant: Substances are classified in Category 2 for reproductive toxicity 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. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.*

In addition to the above criteria it is relevant in the case of dicumyl peroxide to include what the CLP guidance (p. 395) says about how to consider maternal toxicity[4]:

3.7.2.2.1.2. Relevance of specific effects in the parent
All types of reproductive toxic effects may be considered as secondary to parental toxicity. With current knowledge it is not possible to identify specific effects indicating toxicity in parental animals which do not have any relevance to reproductive toxicity (e.g. peroxisome proliferation). However parental toxicity that is less than marked should not influence the classification for reproductive toxicity independent of the specific parental effects observed.

Annex I: 3.7.2.4.2. *Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.*

Discussion:

For dicumyl peroxide no human data is available, so classification in category Repr 1A is not justified.

One prenatal developmental toxicity study in rats is available (performed according to OECD TG 414). Effects were mainly seen in the high dose group, and few or no in the low and medium dose groups.

Maternal toxicity observed as treatment-related clinical signs and treatment-related necropsy findings were observed in some of the dams especially in the high dose group. Only a few of the findings were considered to be adverse by the authors. Therefore, the maternal toxicity seen in the high dose group cannot be characterised as "marked". The one mortality could not with certainty be ascribed to the treatment with the test substance. The laboratory wrote in their report that the dam died due to unclear reasons and in repeat-dose toxicity studies higher doses have not caused any mortality. 5/17 dams had no clinical signs nor necropsy findings. Another 5 dams had salivation and/or alopecia as only clinical signs and no necropsy findings.

Food consumption was reduced in dams in the medium and high dose group. The body weight and body weight gain in the dams was statistically significantly lower in the medium and high dose group than in the control group, in a dose-related manner.

[4] Guidance on the Application of the CLP Criteria Version 4.1 – June 2015

Statistically significant developmental findings, were limited to findings in the high dose group. The following statistically significant effects were seen in the high dose group, when compared to controls: Increased late embryonic death, number of dead foetuses, postimplantation loss and total intrauterine mortality. Fetal body weight was statistically significantly decreased in the high dose group. The incidence of external and skeletal variations and malformations were statistically significantly increased in the high dose goup, compared to the control group.

The REACH registrants ascribe all findings of developmental toxicity in the high dose group to maternal toxicity. However, when scrutinising the individual findings in the full study report it cannot been seen that there is a general correlation between maternal toxicity and developmental effects, see annex 1 and the confidential annex for details. It can not "*be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity*" as it should be according to the CLP guidance in order to not be classified. We consider the developmental toxicity to be independent of the maternal toxicity and not to be a secondary non-specific consequence of the other toxic effects.

According to the CLP guidance, even developmental effects occurring together with maternal toxicity can be the base for classification: "*classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies*" which is the case for dicumyl peroxide as a higher incidence of malformations and embry/foetal lethality was seen in the high dose group.

The database to assess reproductive toxicity of dicumyl peroxide in mammals is limited, and consists of one prenatal developmental toxicity study in rats. No data is available to assess effects on sexual function and fertility. The findings of developmental toxicity, although clear, are limited to the high dose group and no clear dose-response is observed over the range of the three dose groups. The severity and incidence of developmental toxicity in this study may not be enough to warrant classification in category Repr. 1B. However, the findings justify classification in at least category Repr. 2, as evidence of developmental toxicity is available and is supported by our assessment of invidual data that shows that the effects seen in the pups cannot be ascribed to the effects seen in the dams.

In conclusion, we propose that dicumyl peroxide is classificed in **category Repr. 2 (H361d)**. No specific concentration limit is proposed.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The DS did not include studies on adverse effects on sexual function and fertility.

One developmental toxicity study in Wistar rats was performed according to OECD TG 414. No information on the GLP status was included in the CLH dossier. The study findings are summarised in the table below.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Developmental toxicity study (OECD guideline 414) Rats: 24 sperm-positive Wistar rats/treatment	Bis(α,α-dimethylbenzyl) peroxide Purity: 99.0% Oral: gavage 0, 50, 150, 450 mg/kg bw/day	Maternal and developmental NOAEL: 150 mg/kg bw/day Maternal and developmental LOAEL: 450 mg/kg bw/day **Maternal toxicity:** Mortality: **Control, 50 and 150 mg/kg** bw/day dose groups: No mortality	Study report 788.410.4505, Toxi-Coop Zrt. (2014) (not published)

group Reliability score: 1	vehicle: sunflower oil Exposure: Days 5-19 of gestation (daily)	**450 mg/kg** bw/day dose group: one dam died on gestation day 20 (the day of scheduled necropsy) Clinical symptoms: **control group**: alopecia in one female **50 mg/kg** bw/day dose group: no clinical symptoms. **150 mg/kg** bw/day dose group: salivation (4/21 dams). **450 mg/kg** bw/day dose group: No clinical signs in 7/17 dams. Salivation (8/17 dams); piloerection (3/17 dams); alopecia (3/17); reduced activity, vaginal bleeding, pale, cold, hypo tonicity and red colouration around red eye (deceased dam). Necropsy findings: **0, 50 and 150 mg/kg** bw/day dose groups: no necropsy findings. **450 mg/kg** bw/day dose group: No necropsy findings in 11/17 dams. In the remaining dams: enlarged adrenals (4/17 dams); blood in uterus (3/17); enlarged spleen (2/17); uterus filled up with blood (1/17); stomach distended filled up with darker content (1/17); pale liver and pale kidneys (1/17). See confidential annex for individual data. Food consumption: **50 mg/kg** bw/day dose group: a statistically significant temporary decrease in food intake was recorded. **150 and 450 mg/kg** bw/day dose groups: a statistically significant dose related decrease in the food consumption was recorded in the whole treatment period. Body weight: **50 mg/kg** bw/day dose group: a transient decrease in body weight gain. **150 and 450 mg/kg** bw/day dose groups: lower mean body weight, lower corrected body weight, transient weight loss day 5-8 of gestation, and markedly reduced body weight gain and corrected body weight were observed. See annex I and confidential annex for more details. All treatment groups had positive weight gain at the end of treatment period compared with the start weight. **Foetal toxicity:** **50 and 150 mg/kg** bw/day dose groups: no statistically significant effect on the intrauterine development of embryos and foetuses. **450 mg/kg** bw/day dose group: statistically significant increase in the post-implantation loss (17%, 15/17 litters) compared to in the control group (7 %, 14/23 litters). By consequence, the number of viable foetuses in the 450 mg/kg bw/day dose group (9.0/litter) was statistically significantly lower than in the control group (11.6/litter). Furthermore, a statistically significant increase in total intrauterine mortality was observed. The total intrauterine mortality in the high dose group (65 cases) was 29 % of the number of examined corpora lutea, compared to 14% in the control group. Foetal weight: **50 and 150 mg/kg** bw/day dose groups: no statistically significant decrease in the pup's body weight compared with control group. **450 mg/kg** bw/day dose group: increase in percentage of	

		foetuses with decreased body weight (11/17 litters; 31 cases) compared with control group (5/11; 6 cases). External malformations: **50 and 150 mg/kg** bw/day dose groups: no external malformations were observed. **450 mg/kg** bw/day dose group: mal-rotated fore- and hind limbs in six foetuses (5/17 litters; 6 cases; statistically significant) and hydrops fetalis in one foetus. Visceral variations: Hydroureter (bilateral) in 4 pups **50 mg/kg** bw/day dose group: hydroureter (bilateral) in two cases. **150 mg/kg** bw/day dose group: no visceral variations. **450 mg/kg** bw/day dose group: hydroureter (bilateral) in two cases (in two litters). Visceral malformations: four malformations in three pups **control group**: one pup with an absent brain tissue and one with situs intersus totalis **50 mg/kg** bw/day dose group: no visceral malformations. **150 mg/kg** bw/day dose group: one pup with absent lung lobes and with situs intersus totalis. **450 mg/kg** bw/day dose group: no visceral malformations. Skeletal variations: **50 mg/kg** bw/day dose group: incomplete ossified sternum (2 cases; 2/20 litters), incomplete ossification marked of skull bones (2 cases; 2/20 litters), one case of not ossified supraoccipital, thoracic or lumbar centra (3 cases; 3/20 litters) and 7 cases (3/20 litters) of wavy ribs. **150 mg/kg** bw/day dose group: incomplete ossified sternum (8 cases; 5/21 litters), one case incomplete ossification (more than three bones), 4 cases (1/21 litters) of incomplete ossification marked of skull bones, one case of not ossified supraoccipital, thoracic or lumbar centra (2 cases; 2/21 litters) and 16 cases (7/21 litters) of wavy ribs. **450 mg/kg** bw/day dose group: incomplete ossification of skull bones (10 cases; 8/17 litters), incomplete ossified sternum (10 cases; 9/17 litters), metacarpal/metatarsal (4 cases; 4/17 litters), thoracic or lumbar centra (4 cases; 4/17 litters) and wavy (24 cases; 11/17 litters) and marked wavy ribs (6 cases; 5/17 litters). Skeletal malformations: **50 mg/kg** bw/day dose group: no skeletal malformations. **150 mg/kg** bw/day dose group: short and/or bent scapula (3 cases; 2/21 litters). **450 mg/kg** bw/day dose group: short and/or bent scapula (12 cases, 9/17 litters), clavicular (2 cases; 2/17 litters), humerus (9 cases; 7/17 litters), radius (8 cases; 7/11 litters) and ulna (5 cases; 5/17 litters).	

One developmental toxicity study in rats had been performed with exposure to bis(α,α-dimethylbenzyl) peroxide, and the maternal and foetal toxicity findings are presented in the table above.

The table below shows the groups and number of animals/foetuses included and analysed in the study.

Dose (mg/kg bw/day)	**0**	**50**	**150**	**450**
Number of females	24	24	24	23 (1 mortality on day 20)
Number of females with pregnant uteri, necropsied	23	20	21	17
Number of foetuses necropsied for skeletal examination	133	109	114	76

Animals treated with bis(α,α-dimethylbenzyl) peroxide exhibited increased signs of toxicity from the low dose (transient decrease in food consumption and body weight gain) to the high dose, where adverse clinical symptoms some necropsy findings, weight loss, markedly reduced body weight gain, and reduced food consumption were observed. These effects were marked in dams of the highest treatment group (450 mg/kg bw/day) and this dose is considered a LOAEL for maternal effects.

Mortality, clinical symptoms, necropsy

One dam died in the 450 mg/kg bw/day dose group on gestation day 20 (the day of scheduled necropsy) with the following adverse clinical symptoms: vaginal bleeding, piloerection, paleness, coldness and hypotonicity. However, there were no pathological examination data of the foetuses from the deceased dam: usually examination of foetuses from deceased dams is conducted when the death occurs on the day of scheduled necropsy. The death was considered by the performing laboratory to be treatment related, although it was stated in the study report that the dam "died due to unclear reason". No mortality was observed in the 50 and 150 mg/kg bw/day dose groups.

No clinical observations were noted for the dams in the 50 mg/kg bw/day dose group. The only clinical sign in the 150 mg/kg bw/day dose group was salivation, seen in four (4/21) dams. Salivation was seen in eight dams (8/17 dams) in the 450 mg/kg bw/day dose group. Salivation was judged to be treatment-related however, it was not considered an adverse effect. In the 450 mg/kg bw/day dose group, 1/17 dams had vaginal bleeding, 3/17 had piloerection and 1/17 was hypotonic. These were considered adverse clinical signs and an effect of the test item.

Necropsy findings in the high dose group were: 4/17 dams had enlarged adrenals and bloody uterine content (blood in the uterus (2/17 dams), blood in uterine horn (1/17 dam) and uterus filled with blood (1/17 dam)). One dam had an enlarged spleen. These findings were considered to be treatment related. There were no necropsy findings in the remaining 11/17 dams examined in the high dose group.

Overall, a majority of the examined dams did not have adverse clinical symptoms, and only 4/17 dams (23%) had both adverse clinical signs and necropsy findings, while 5/17 dams (29%) had no adverse clinical signs and no necropsy findings. Another 5 dams (29%) had salivation and/or alopecia as only clinical signs and no necropsy findings.

Food consumption

Evaluation of food consumption data showed that there was a test substance treatment related decrease in the average food intake in the 150 and 450 mg/kg bw/day dose groups and a temporary decrease in the average food intake in the 50 mg/kg bw/day dose group. The food consumption reduction in the 150 mg/kg bw/day dose group, although statistically significant, was judged not to be adverse and was considered biologically non-relevant since the lower food consumption only resulted in a small reduction of body weight (less than 10% lower than the control group). When the individual food consumption data for the dams in the high dose group were compared with the data for observed clinical signs and its adversity, there was no clear correlation between lower food intake and adverse clinical symptoms.

Body weight

Evaluation of the body weight parameters showed a dose-dependent decrease in all recorded body weight parameters, for the 150 and 450 mg/kg bw/day dose groups. The decrease in the body weight parameters were considered to be related to the test item. Further, a transient reduced body weight gain was noticed in the 50 mg/kg bw/day dose group and it was considered to be a non-adverse effect. In the 150 mg/kg bw/day group the body weight reduction at the end of treatment was less than 10% lower than the control group, however body weight gain was reduced by 15%. The dams of the high dose group had a body weight at the end of treatment that was 17% lower than the control dams, however the body weight gain was about half of the gain seen in the control group. At the end of the treatment period, all dams in all treatment groups gained some weight compared with the start weight.

The body weight parameters of the dams with adverse clinical signs did not differ with statistical significance from the dams without such signs. Thus, reduction both in food intake and body weight gain alone could not explain the observed clinical signs and necropsy findings.

Toxicity in pups

In the 450 mg/kg bw/day dose group, examination of the dams showed a statistically significant increase in post-implantation loss (17%, 15/17 litters) compared with the control group (7%, 14/23 litters). There were 32 cases of post-implantation loss. Ten of these cases occurred in five dams without clinical or necropsy findings.

A statistically significant decrease in the number of viable foetuses was observed in the high dose group and this was considered treatment related. Furthermore, a statistically significant increase in total intrauterine mortality was observed. There were 65 cases of intrauterine mortality (29% vs 14% in the control groups). Five dams with no clinical signs or necropsy findings had 20 cases (20/65) of the total intrauterine mortality; i.e., ~1/3 of the total intrauterine mortality was found in dams without any adverse clinical symptoms or necropsy findings.

This suggests that post-implantation loss and increased intrauterine mortality was not related to maternal clinical symptoms nor necropsy findings in the dams and thus raises a concern for the developmental effects of bis(α,α-dimethylbenzyl) peroxide.

Furthermore, there was an increase in the percentage of foetuses with body weight retardation in the 450 mg/kg bw/day dose group (11/17 litters; 31 cases) compared with the control group (5/23; 6 cases). These observations could not be explained by maternal toxicity, since several dams without adverse clinical signs, necropsy findings, or drastically reduced

body weight or food intake, had foetuses with decreased body weight. There was no difference in the incidence of pups with decreased body weight in the 50 (5/20 litters; 5 cases) and 150 (7/21 litters; 8 cases) mg/kg bw/day dose groups compared with the control group (5/23 litters; 6 cases).

External examination of the pups in the 450 mg/kg bw/day dose group showed malrotated fore- and hind limbs in six foetuses (5/17 litters; 6 cases, statistically significant) and hydrops fetalis in one foetus. This was considered to be treatment related. Of the six cases with malrotated fore- and hind limbs, none of them were from the 3/17 dams with adverse clinical symptoms, and 3/6 cases were from two dams with no clinical and necropsy findings.

There was a high incidence of foetuses with skeletal malformations in the 450 mg/kg bw/day dose group: short and/or bent scapula (12 cases, 9/17 litters), clavicular (2 cases; 2/17 litters), humerus (9 cases; 7/17 litters), radius (8 cases; 7/11 litters) and ulna (5 cases; 5/17 litters). In the 150 mg/kg bw/day dose group, short and/or bent scapula (3 cases; 2/21 litters) were recorded. This high incidence of malformations, without marked maternal toxicity, is sufficient to raise a concern about the developmental effects of bis(α,α-dimethylbenzyl) peroxide.

In the 450 mg/kg bw/day dose group, there was a statistically significant increase in the incidence of skeletal variations such as incomplete ossification of skull bones, incomplete ossified sternum, metacarpal/metatarsal, and wavy and marked wavy ribs, and these incidences occurred without adverse maternal toxicity. Similarly, in the 150 mg/kg bw/day dose group, some variations were observed without clear correlation to maternal clinical signs.

Maternal toxicity is apparent in the present study, but there is no clear connection between maternal toxicity and foetal malformations, not even in the high dose group. This indicates that the developing foetuses are more sensitive than the dams to exposure to the test substance. The evaluation of the presented data supports the conclusion that the observed developmental effects following the exposure to bis(α,α-dimethylbenzyl) peroxide are not secondary non-specific consequences of maternal toxicity.

The DS proposed to classify bis(α,α-dimethylbenzyl) peroxide as Repr. Cat. 2; H361d.

Comments received during public consultation

Three MSCAs agreed with the DS proposal for classification in Repr. Cat. 2 for development.

There was disagreement from the company-manufacturer, based on limited evidence only seen from the high dose group and no clear dose-response relationship was observed. In addition, the company-manufacturer pointed out that, marked maternal toxicity was apparent in the high dose group and this may account for the foetal toxicity. A testing proposal related to a PND study in the rabbit as a second species is ongoing. The study may be available within 1 year, therefore the company argued that the assessment for teratogenicity should be discussed when the data are available.

Assessment and comparison with the classification criteria

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. For bis(α,α-dimethylbenzyl) peroxide findings concerned developmental toxicity, which was described in the CLP Annex 1: 3.7.1.4 "Adverse effects on development of the offspring".

Only one prenatal developmental toxicity study in rats was available, performed according to OECD TG 414.

The table below shows the maternal toxicity findings.

Effects	Control	50 mg/kg bw/d	150 mg/kg bw/d	450 mg/kg bw/d
Mortality	0	0	0	1
Salivation	0	0	4/21	8/17
Piloerection	0	0	0	3/17
alopecia	0	0	0	3/17
Clinical signs: (Reduced activity, vaginal bleeding, pale, cold, hypotonicity, red colouration around eye)	0	0	0	10/17
Necropsy finding Enlarged adrenals Blood in uterus Enlarged spleen Uterus filled with blood Stomach distended fill up Pale liver Pale kidney	0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0	6/17 4/17 3/17 2/17 1/17 1/17 1/17 1/17
Food consumption	None	A statistically sign. temporary decrease was recorded.	Statistically sign. decrease was recorded	Statistically sign. decrease was recorded
Body weight Start weight (g) Weight day 11 (g) Weight day 20 (g) Body weight gain (g)	 236 ± 20.7 267.3 ± 21.5 338.7 ± 27.6 102.7 ± 14.7	 236.8 ± 14.9 265.3 ± 16.3 335.8 ± 20.7 99 ± 13.1	 233.1 ± 10.7 **254. 8 ± 13.1*** **321.2 ± 14.5**** **88 ± 12.8****	 234.1 ± 11.0 **246.3 ± 15.2**** **283.6 ± 24.5**** **49.5 ± 20****

** p<0.01

Body weight: The DS argued that the observed body weight parameters of the dams with adverse clinical signs did not differ statistically significantly from the dams without such signs. Thus, reduction in food intake and body weight gain alone could not explain the observed clinical signs and necropsy findings. In addition, no corrected body weight values were given, and the dams at high does had an average of 9.0 pups per litter which was statistically significantly lower than in the control group (11.6/litter). Furthermore, the high dose pups had a lower mean foetal weight, 2.9 vs 3.3 g in the control group. The lower number of pups and their lower weight may explain the lower uncorrected body weight.

RAC identifies the following observations as relevant for the assessment of the developmental toxicity/ teratogenicity classification.

Effects	Control	50 mg/kg bw/d	150 mg/kg bw/d	450 mg/kg bw/d
Pre implantation loss	7%	12%	9%	**14%****
Post implantation loss	7% (14/23 litters)	4%	5%	**17%** (15/17 litters)**
Late embryonic death	1%	1%	1%	**12%****
Dead foetuses	0%	0%	0%	**3%****
Total intrauterine mortality	14%	16%	13%	**29%****
External examination				
Foetuses with abnormalities	2.5%	2.3%	3.5%	**26.2%****

Variations	2.5%	2.3%	3.5%	**21.5%****
Malformations	0%	0%	0%	**4.7%****
Visceral examination				
Foetuses with abnormalities	1.3%	2%	1%	2%
Skeletal examination				
Foetuses with abnormalities	19.4%	15%	22.7%	**61.4%****
Variations	17.8%	15%	19.9%	**39.8%****
Malformations	1.6%	0%	2.9%	**21.6%****
Type of skeletal abnormalities, variations				
Skull				
Incomplete ossification, marked (> three bones)	1%	0%	0%	1%
Incomplete ossification, marked (1 bone or more)	2%	2%	4%	**13%****
Supraoccipital not ossified	0%	1%	1%	1%
Hyoid not ossified	1%	0%	0%	1%
Sternebrae				
Three or less ossified	4%	2%	7%	**13%****
Misaligned	1%	0%	0%	0%
Bipartite	0%	0%	0%	1%
Ribs				
Wavy	6%	6%	**14%***	**32%****
Wavy, marked	0%	1%	1%	**8%****
Type of skeletal abnormalities, malformations				
Sternebrae				
Xiphoid split	1%	0%	1%	3%
Vertebrae, thoracic centra				
thoracic bipartite cartilage dumb-bell shaped	2%	0%	0%	0%
Pectoral girdle				
Scapula bent and/or short	0%	0%	3%	**16%****
Clavicula bent and/or short	0%	0%	0%	2%
Forelimbs				
- Humerus bent and/or short	0%	0%	0%	**12%****
Ulna bent and/or short	0%	0%	0%	**8%****
Radius bent and/or short	0%	0%	0%	**11%****
Hind limbs				
Femur short, bent	0%	0%	0%	**5%****
Tibia bent and/or short	0%	0%	0%	3%
Fibula bent and/or short	0%	0%	0%	**4%***

** ($p<0.01$)

A statistically significant decrease in the number of viable foetuses was observed in the high dose group and this was considered treatment related by the DS. Furthermore, a statistically significant increase in total intrauterine mortality was observed (65 cases of intrauterine mortality). Five dams with no clinical signs or necropsy findings had 20 (~1/3) cases of total intrauterine mortality. This suggests that post-implantation loss and increased intrauterine mortality may not be related to maternal clinical symptoms.

Toxic effects of the substance were noted in both the dams and the foetuses of the high dose group at 450 mg/kg bw/d. There was an increase in some clinical signs as well as reduced body weight, body weight gain, reduced food intake and some necropsy findings in the dams of the high dose group compared to the control group.

There was also a clear effect of the test substance on the foetuses of the high dose group, manifested as increased intrauterine mortality, lower foetal weight and an increase in the incidence of variations and malformations in the pups in the high dose group compared to the control group.

There was a statistically significant increase in post implantation loss, late embryonic death, foetal death and a statistically significant reduction in number of viable foetuses in the high dose group. However, the DS assessed the relationship between the individual dams with symptoms of maternal toxicity and the individual pups showing skeletal abnormalities or with a high incidence of intrauterine mortality including post implantation losses. Regarding intrauterine mortality, the DS reported that it was not possible to relate the higher incidences to the maternal toxicity. When the findings were studied on an individual basis it was seen that there was no clear correlation between the dams with clinical signs of toxicity and/or necropsy findings and the intrauterine mortality. Therefore, these findings cannot be ascribed to maternal toxicity and RAC considers the implantation losses and the total intrauterine mortality to be related to the substance administration.

The observations of skeletal malformations, including the statistically significant higher incidences of effects in the pectoral girdle, the forelimbs and the hind limbs, were specific and could not be explained only by maternal toxicity.

Placing greater weight, both on the increased intrauterine mortality and on the specific effects observed from the skeletal malformations, and with the comparisons of the individual dam/litter data between maternal toxicity and foetal toxicity showing no correlation, then the observed teratogenicity / developmental toxicity was not secondary to the maternal toxicity. Overall RAC considered that the criteria for classification for developmental toxicity were met for a presumed human reproductive toxicant, thus bis(α,α-dimethylbenzyl) peroxide warrants classification as **Repr. 1B; H360D**.

Supplemental information - In depth analyses by RAC

The table below contains a summary of the individual dams observations regarding clinical symptoms, necropsy findings, the incidence of malformations, post implantation losses and the total intrauterine mortality. The green colour represents the animals with very slight maternal toxicity, the yellow moderate maternal toxicity and the red, high maternal toxicity.

Dam id. No.	Clinical symptoms	Necropsy findings	Malformations / Liter	Postimpl.loss (%)	Totale intraut.mortality (%)
0122148	Salivation g.d. 12-16	No	4	14	50
0223156	Salivation g.d. 13-14; 16-19	No	6	8	15
0324159	Salivation g.d. 15-19	No	0	9	9
0425173	Salivation, piloerection, reduced activity, red coloration around right eye.	No	4	0	9
0545104	Alopecia neck, salivation gd. 15	No	0	9	9
0646112	Alopecia (neck, left side and on the nose), salivation	No	0	23	23
0747116	None	No	1	14	25
0484126	Piloerction, reduced activity, pale, vaginal bleeding, hypotonicity, cold.	Enlarged spleen, slight stomach filled up, distended, darker content.	0	30	46
0949129	None	No	0	36	42
1050171	None	No	2	8	21
1151183	None	No	0	30	50
1252187	None	No	7	0	7
1353107	None	Uterus filled up with blood, enlarged adrenals.	0	0	17
1454138	None	Pale liver, pale kidneys.	3	73	75
1555144	Alopecia (abdomen)	Blood in uterine horn, enlarged adrenal right.	0	9	23
1655182	Salivation g.d. 11-15	Blood in uterus, enlarged adrenals.	8	17	23
1757205	Salivation g.d. 11-15, piloerection g.d. 15	Blood in uterus, enlarged adrenals.	5	13	53
1800161 +	Vaginal bleeding, piloerection, pale, cold, died on g.d. 20	Bloody vaginal orifice, enlarged spleen, enlarged adrenals.	--	--	--

10.10.7 Adverse effects on or via lactation

Not relevant for this dossier

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

Not relevant for this dossier.

10.10.9 Comparison with the CLP criteria

Not relevant for this dossier

10.10.10 Conclusion on classification and labelling for reproductive toxicity

This developmental study indicates that treatment of rats with dicumyl peroxide causes only moderate toxicity in dams, however at high doses the substance causes developmental effects which include increase in postimplantation loss and intrauterine mortality, external and skeletal variations and malformations in the foetuses. Based on the available study, **a classification of dicumyl peroxide for Repr 2-H361d** is justified

due to the developmental effects seen in pups to dicumyl peroxide exposure without marked maternal toxicity.

10.11 Specific target organ toxicity-single exposure

Not evaluated for this dossier.

10.12 Specific target organ toxicity-repeated exposure

Not evaluated for this dossier.

10.13 Aspiration hazard

Not evaluated for this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated for this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated for this dossier.

13 ADDITIONAL LABELLING

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14 REFERENCES

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15 ANNEXES

Annex I to the CLH report

Confidential annex.