Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.

EC Number: 308-208-6
CAS Number: 97925-95-6

CLH-O-0000001412-86-166/F

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

22 September 2017

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.

EC Number: **308-208-6**

CAS Number: **97925-95-6**

Index Number: **-**

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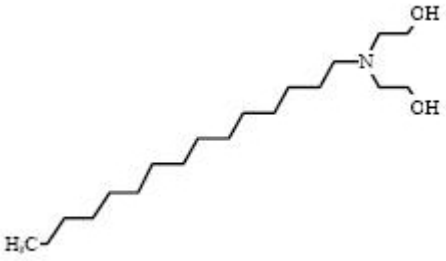
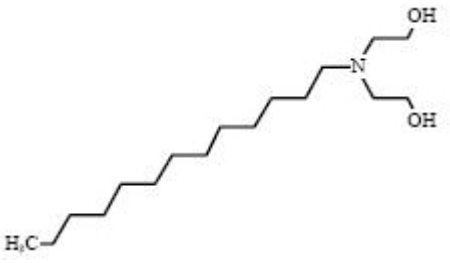
Version number: 5 **Date: 12-10-2016**

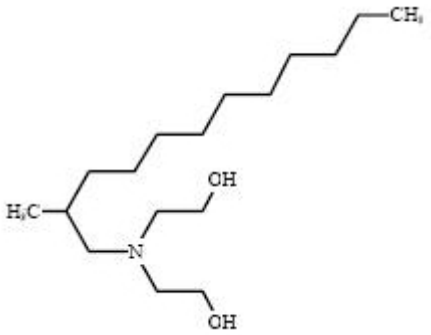
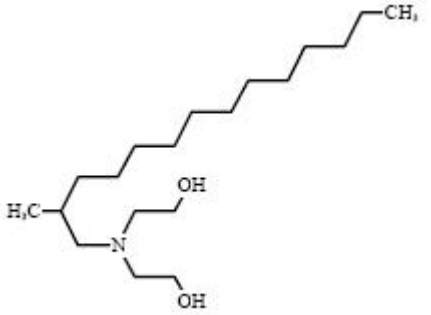
CONTENTS

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)	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.
Other names (usual name, trade name, abbreviation)	
ISO common name (if available and appropriate)	
EC number (if available and appropriate)	308-208-6
EC name (if available and appropriate)	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.
CAS number (if available)	97925-95-6
Other identity code (if available)	
Molecular formula	
Structural formula	Ethanol, 2,2'-iminobis-, N-pentadecyl  Ethanol, 2,2'-iminobis-, N-tridecyl  Ethanol, 2,2'-iminobis-, N-methyldodecyl

	 Ethanol, 2,2'-iminobis-, N-methyltetradecyl 
SMILES notation (if available)	
Molecular weight or molecular weight range	> 287.0 < 315.0
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)	Confidential
Degree of purity (%) (if relevant for the entry in Annex VI)	100%

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)**
Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.	100%	Not classified	Acute Tox 4 (oral) Skin Corr. 1C Eye Dam. 1 Repr 2 Aquatic acute 1 Aquatic chronic 1
Ethanol, 2,2'-iminobis-, N-pentadecyl	>10 - <25% (w/w)	No entry	No entry

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)**
Ethanol, 2,2'-iminobis-, N-tridecyl	> 25 - < 50% (w/w)	No entry	No entry
Ethanol, 2,2'-iminobis-, N-methyldodecyl	> 25 - < 50% (w/w)	No entry	No entry
Ethanol, 2,2'-iminobis-, N-methytetradecyl	>10 - <25% (w/w)	No entry	No entry

All studies in this report were performed with the registered substance as presented in Table 2.

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

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

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	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	-										
Dossier submitters proposal		Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.	308-208-6	97925-95-6	Repr. 1B	H360D	GHS08 Dng	H360D			
Resulting Annex VI entry if agreed by RAC and COM		Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.	308-208-6	97925-95-6	Repr. 1B	H360D	GHS08 Dng	H360D			

Table 6: 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	*hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	*hazard class not assessed in this dossier*	No
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		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

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance has no previous harmonized classification and labelling.

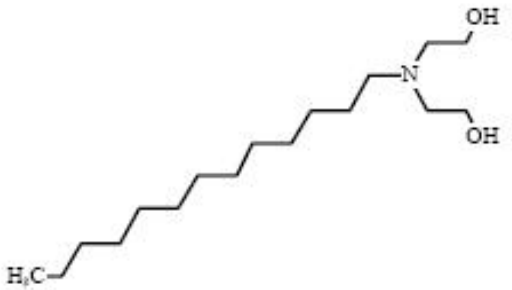
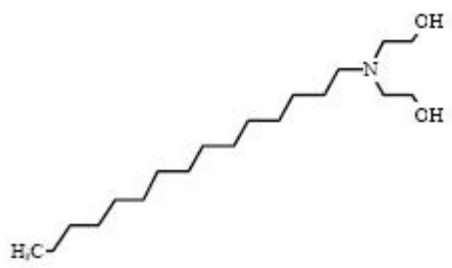
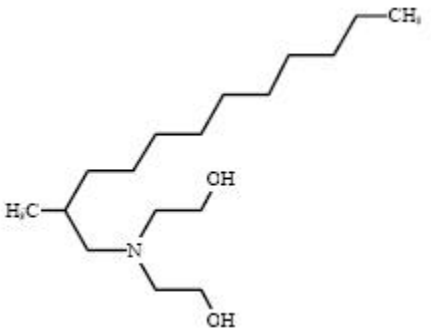
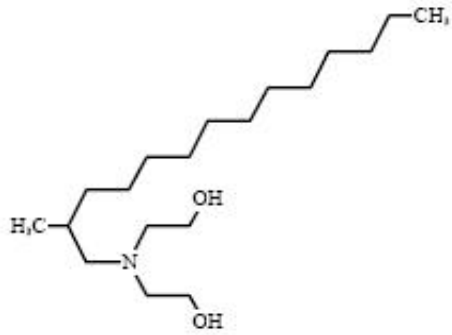
4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[A.] There is no requirement for justification that action is needed at Community level.

RAC general comment

The present Opinion only addresses reproductive toxicity since this was the sole endpoint that was evaluated by the dossier submitter (DS) in their proposal.

Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. is an UVCB. Its constituents and their concentration range are:

Ethanol, 2,2'-iminobis-,N-tridecyl, > 25 - < 50% (w/w) 	Ethanol, 2,2'-iminobis-,N-pentadecyl, >10% - <25% (W/W) 
Ethanol, 2,2'-iminobis-, N-methyldodecyl, > 25 - < 50% (w/w) 	Ethanol, 2,2'-iminobis-, N-methyltetra-decyl, >10 - <25% (w/w) 

None of the individual constituents has a REACH registration and no information on their individual toxicological properties is available according to the DS.

5 IDENTIFIED USES

The substance is used in the manufacture of plastics products, including compounding and conversion.

6 DATA SOURCES

ECHA dissemination site

The Chemical Safety Report

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Extremely pale yellow liquid	(Walker, J.A., Croda Europe Ltd., 2010)	
Melting/freezing point	3 °C	(Nugerman, S., Croda Europe Ltd., 2010)	
Boiling point	The substance decomposes before reaching the boiling point.		
Relative density	0.907 g/cm³ at 20 °C	(Nugerman, S., Croda Europe Ltd., 2010)	
Vapour pressure	0.031 Pa at 25 °C	(Walker, J.A., Croda Europe Ltd., 2010)	
Surface tension	49.05 dyne/cm at 20 °C (limit of water solubility) 29.00 dyne/cm at 20 °C (saturated solution)	(Calvert, M.E., Croda Europe Ltd, 2010)	
Water solubility	80.8 mg/L at 20 °C ± 0.5 °C, pH 6.9-7.2	(Walker, J.A., Croda Europe Ltd., 2010)	
Partition coefficient n-octanol/water	log Kow 4.39 (C13) - 5.37 (C15)	(EPIWIN calculation, 2010)	
Flash point	202 °C at 1000-1010 mbar	(Nugerman, S., Croda Europe Ltd., 2010)	
Flammability	Non flammable		Based on chemical structure pyrophoricity and flammability in contact with water are not expected.
Explosive properties	Non explosive		In accordance with column 2 of regulation (EC) No 1907/2006 (REACh) Annex VII, the explosiveness of the substance does not need to be tested, because there are no chemical groups associated with explosive properties in the molecule.
Self-ignition temperature	No auto-ignition expected.		The substance is a liquid, non flammable in air, with no flash point up to 200 °C.
Oxidising properties	Non oxidising		The substance is incapable of reacting exothermically with combustible materials, for

Property	Value	Reference	Comment (e.g. measured or estimated)
			example on the basis of the chemical structure. In the case of this particular substance there are no chemical groups associated with oxidising properties present in the molecule.
Granulometry	Testing is not necessary because the substance is a liquid.		This substance is a liquid and as such it is marketed in a non granular form. There is no risk of forming respirable dust or the risk of dust explosion.
Stability in organic solvents and identity of relevant degradation products	Not applicable		The stability of the substance in organic solvents is not considered as critical.
Dissociation constant	pKa1: 5.8 at 20 °C pKa2: 15.45 at 20 °C	(SPARC calculation, 2010)	
Viscosity	182 mm²/s at 20 °C; 57.6 mm²/s at 40 °C (OECD 114, capillary method)	(Wooley AJ, Harlan laboratories, 2012)	

All references as summarised in the registration dossier.

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
The toxicokinetic behaviour of Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs (CAS-No. 97925-95-6) was assessed. The OECD QSAR Application Toolbox was used to make a qualitative prediction of the metabolites formed in liver, skin and gastrointestinal tract. The fate of these metabolites is predicted on the basis of their chemical structure based on expert judgement.	Metabolites identified: yes Details on metabolites: No information is available regarding the metabolism of the substance specifically. The potential metabolites of a closely related substance (CAS No. 68155-05-5, side chain length n = 9-15) in liver, skin and gastrointestinal tract were simulated using the QSAR OECD Toolbox 1.1.02. 23 hepatic metabolites were predicted. These metabolites arise from hydroxylation, N-dealkylation, and oxidation, especially beta-oxidation of intermediary fatty acids. The main reaction is most likely a dealkylation, to diethanolamine and a primary alcohol. The alcohol is typically further metabolized to a fatty acid that	2 (reliable with restrictions) key study Assessment of toxicokinetic behaviour Test material (CAS number): 71768-60-2	DR. KNOELL CONSULT GmbH (2010)

Method	Results	Remarks	Reference
	enters into fatty acid catabolism, and is ultimately metabolized to carbon dioxide and water.		

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Absorption

The absorption has not been quantified; however, using the Danish QSAR database, the gastrointestinal absorption of a closely related substance (CAS No. 68155-05-5) was predicted to be 100% (1 mg dose). As the substance is a corrosive substance, no acute dermal or inhalation toxicity studies were performed. The bioavailability via the dermal route has thus not been examined experimentally. Considering the corrosive nature of the substance, it is reasonable to assume that exposure may cause damage to the skin, subsequently facilitating dermal uptake. Using the Danish QSAR database, the dermal absorption of a similar substance (CAS No. 68155-05-5) was estimated to be 0.00400 mg/cm²/event, which is relatively low. It is likely that the corrosive effect increases bioavailability due to a loss of skin barrier integrity. For risk assessment purposes, the bioavailability via the inhalation route is considered to be similar to that of the oral route, i.e. quantitative.

Metabolism

No information is available regarding the metabolism of the substance specifically. The potential metabolites of a closely related substance (CAS No. 68155-05-5) in liver, skin and gastrointestinal tract were simulated using the QSAR OECD Toolbox 1.1.02. 23 hepatic metabolites were predicted. These metabolites arise from hydroxylation, N-dealkylation, and oxidation, especially beta-oxidation of intermediary fatty acids. The main reaction is most likely a dealkylation, to diethanolamine and a primary alcohol. The alcohol is typically further metabolized to a fatty acid that enters into fatty acid catabolism, and is ultimately metabolized to carbon dioxide and water. Diethanolamine is readily metabolized to monoethanolamine, which is known to be a part of the phospholipid synthesis pathway (see the KEGG database, www. genome.jp). In repeated dose studies on rats, exposure to diethanolamine bioaccumulated in (among other) liver and kidney tissue lead to increasing levels of aberrant phospholipids and histopathological lesions (Knaak JB et al, 1997; Mathews JM et al, 1995). As the subchronic rat and dog studies did not reveal any significant histopathological changes in liver or kidneys, the bioaccumulation of diethanolamine as a metabolite of ethanol, 2,2’-iminobis-, N-(C13-15-branched and linear alkyl) derivs is not expected to occur under experimental dosing conditions. In the skin, two metabolites were predicted, with one or two carboxy groups. These are expected to be metabolized via the same pathways as described for the liver metabolism.

Excretion

The substance has a molecular weight lower than 500 u and is relatively water soluble. The QSAR simulation furthermore predicts that ethanol, 2,2’-iminobis-, N-(C13-15-branched and linear alkyl) derivs will primarily be metabolised to molecules that are utilized in well-known human metabolic pathways. Therefore, the substance is likely to be excreted as breakdown products of these metabolic pathways. The secondary route of excretion is expected to be via the urine, including any minor hepatic metabolites.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

Not evaluated in this dossier.

10.4 Skin corrosion/irritation

Not evaluated in this dossier.

10.5 Serious eye damage/eye irritation

Not evaluated in this dossier.

10.6 Respiratory sensitisation

Not evaluated in this dossier.

10.7 Skin sensitisation

Not evaluated in this dossier.

10.8 Germ cell mutagenicity

Not evaluated in this dossier.

10.9 Carcinogenicity

Not evaluated in this dossier.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

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

There are no studies available that specifically investigated effects on sexual function and fertility.

In the 90 day Repeated Dose Toxicity Studies performed in two different species, rats (Exp Key Repeated dose toxicity: oral.003) and dogs (Exp Key Repeated dose toxicity: oral.002), ovaries, testes with epididymides, uterus with vagina and cervix, mammary gland and prostate were examined macro-and microscopically. No effects on reproductive organs were found. For a more detailed description of the repeated dose studies, see paragraph 10.12.

10.10.3 Comparison with the CLP criteria

No relevant or treatment-related changes on reproductive organs were found in repeated dose studies in rats and dogs, nor in a pre-natal developmental toxicity study in rats. There are no studies

available that determined effects on sexual performance or fertility. Thus, no classification is proposed for sexual function and fertility based on absence of data.

10.10.4 Adverse effects on development

Table 9: 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
Prenatal Developmental Toxicity Study (OECD 414), rats, RccHan™: WIST(SPF), 22 females/dose	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs., 10, 30 and 90 mg/kg bw/day, Duration of exposure: Day 6 - Day 20 post coitum (p.c.)	Maternal toxic effects: high dose: decrease in body weight/gain (-7%/-14%), decrease in food consumption (-10%) Maternal LOAEL 90 mg/kg bw/day, NOAEL 30 mg/kg bw/day Embryotoxic/teratogenic effects: high dose: post-implantation loss (80/265), external abnormalities of head (5 (2.7%)), decrease in fetus bodyweight (-4%), altered texture of cut surface of eye lens (58 (60%)), cervical vertebra and cranial bone abnormalities (7 and 5 (8 and 6%)); medium dose: altered texture of cut surface of eye lens (31 (23%)), cervical vertebra abnormalities (3 (3%)) Developmental toxicity LOAEL: 30 mg/kg bw/day, NOAEL 10 mg/kg bw/day	Exp Key Developmental toxicity / teratogenicity.002, 2014, registration dossier

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

A prenatal developmental toxicity study (OECD 414) is available. In this study, 22 pregnant rats were exposed to the test substance in doses of 10, 30, and 90 mg/kg bw/day daily from day 6 - day 20 post coitum (15 days). Significant maternal effects were only observed at 90 mg/kg bw/day and consisted of decreased body weight gain (day 21: mean 30±11% compared to 44±6% in the control group) and decrease in food consumption. Mean body weight gain was statistically significantly reduced on days 4 and 7 to 8 p.c. and from day 10 p.c. until the end of the study. Corrected body weight gain was reduced without statistical significance (mean +6.6% compared to +10.7% in the control group). Absolute body weight was statistically significantly decreased from day 19 p.c. onwards. These reductions were considered to be test item-related. No maternal mortality occurred and no clinical signs or macroscopic findings were observed. An overview of the maternal effects is given Table 1 of Annex 1.

Several fetotoxic effects were reported at 30 and 90 mg/kg bw/day.

In the high dose group, a statistically significant increase in post-implantation loss was recorded (control 7 (2.6% of implantation sites), low dose 4 (1.3%), mid dose 10 (3.9%), high dose 80 (30.2%) of implantation sites) (Annex 1, Table 2). This resulted in a statistically significant

decrease in the mean number of fetuses per dam, when compared to control animals (high dose: 9.3 fetuses per dam; control: 12.6 fetuses per dam).

There was a higher incidence of fetuses with external abnormalities seen in the high dose group, with 5 fetuses in 4 litters affected (Annex 1, Table 3). All abnormalities were of the head including slightly misshapen head, no skin over head, missing eyes and nasal opening, cleft lip and clear membrane over part of head. Although all fetuses were not affected by the same abnormality, a possible association to treatment could not be ruled out. No abnormal findings were recorded for the control and medium dose group. In the low dose group a shortened lower jaw and a closed mouth was recorded.

Visceral examinations were performed on half of each litter (Annex 1, Table 4). The fetuses were preserved in Bouin's fixative and stored in containers with 94% ethanol. A gross examination was performed of the brain and all other internal organs including the internal structure of the eyes, heart and kidneys. Eye defects are determined by examination of cut slices of approximately 1 mm thickness of the head under low powered magnification. The results showed a dose-dependant increase in the incidence of alterations of the texture of the cut surface of the eye lens (control: 0/137 (0%), low dose: 9/153 (6%), medium dose: 31/133 (23%), high dose: 58/97 (60%) of fetuses examined). Although this effect is usually concidered a process artifact, the dose dependency and high incidences in the mid/high dose groups suggest it is substance related. According to the registrant, the effect could still be a process artifact with the explanation for a dose response being that the eyes were examined by dose group with the lowest group being processed first and so less affected by the storage fluid. As it is not indicated in the study report in which order the fetuses were examined, this possibility cannot be confirmed nor denied. Bouin's fixative is commonly used as a fixative, but has the disadvantage it is very reactive. However, no indications could be found that this reactivity leads to alteration of the texture of the surface of the lens in the course of a study (the study duration was appr. 2 weeks).

An increase in cervical vertebra abnormalities was reported in the mid and high dose groups, with 0, 1, 3 and 7 incidences seen in 0, 1, 3 and 7 litters at 0, 10, 30 or 90 mg/kg bw/day, respectively. At the high dose, incidences were increased of cranial bone abnormalities (n=5, 6%), a long ventral plate (variation), incomplete ossification in the cranium as well as supernumerary rudimentary ribs. In addition, variations of the ribs (cervical rib and wavy rib) as well as fused costal cartilages were outside the range of the historical control data in the high dose group and were therefore considered to be test item-related (Annex 1, Table 5).

In the mid and high dose groups, the mean body weights calculated on an individual basis of the male and female fetuses combined (control: 4.9 ± 0.4 g; low dose: 4.8 ± 0.4 g; medium: 4.7 ± 0.5 g, high dose: 4.7 ± 0.4 g) as well as for the male fetuses in the high dose group (control: 5.0 ± 0.4 g; high dose: 4.8 ± 0.4 g), were slightly but statistically significantly reduced.

For a more detailed overview of this study, please consult Annex I.

10.10.6 Comparison with the CLP criteria

Several severe fetotoxic effects were reported in a pre-natal development study in rats, including post-implantation loss, external abnormalities of the head, altered texture of the cut surface of the eye lens, cervical vertebra and cranial bone abnormalities at the highest dose. The effects were dose-related, with a LOAEL of 30 mg/kg bw/day.

At the mid-dose of 30 mg/kg bw/day, an increase of altered texture of the cut surface of the eye lens and of cervical vertebra abnormalities were observed.

The altered texture of the cut surface of the eye lens is considered treatment related because of the clear dose effect relation and because macroscopic and microscopic cateracts were observed at 150 mg/kg bw/day in the 90-day study showing the capability of this substance to affect the eye. Considering the severity of the effect on the eye lens in the 90-day study it is assumed that the observed effect in the developmental study is also severe. As effects on the eye lens were observed in the 90-day study at 150 mg/kg bw/day but most likely not at 30 mg/kg bw/day whereas effects on the eye lens were observed at 30 and 90 mg/kg bw/day in the developmental study (2 weeks exposure), the results indicate that developing animals may be more susceptible to the effects of this substance on the eye lens. No effect on the eyes was observed in the 90-day dog study, except unilateral lateral mucoid lacrimation in one high dose female (100 mg/kg bw/day), which was considered incidental.

Maternal toxicity was limited to decreased food consumption (-10%) and reduced body weight gain (-14%) at the highest dose of 90 mg/kg bw/day. However, these maternal effects are most likely largely secundary to the post-implantation loss of 30% and the reduced body weight of the pups (-4%). This is confirmed by the small and statistically non-significant reduction in corrected body weight gain (mean +6.6% compared to +10.7% in the control group). In addition, the available 90-day repeated dose toxicity study by gavage shows that this substance only induces local effects to the stomach due to its corrosivity at 150 mg/kg bw/day and secondary systemic effects likely related to the stomach effects including possibly mortality. Direct systemic effects were limited to a high incidence of cateracts (46% in the high dose group).

No maternal toxicity was observed in the developmental study at 30 mg/kg bw/day. The toxicological effects at 30 mg/kg bw/day in the females in the 90-day study were limited to local stomach iritation and related secondary effects including possibly mortality. There were no direct systemic effects.

The severe developmental effects observed at 90 mg/kg bw/day are considered unlikely to be secondary to the observed reduced body weight gain and food intake as these maternal effects were only small and likely caused by local irritation of the stomach. A small decrease in body weight gain does not normally result in an increase in post-implantation loss or other developmental effects as even an absolute reduction in body weight due to feed restriction does not result in an increase in post-implantation loss (Fleeman, 2005).

The severe developmental effects observed at 30 mg/kg bw/day occurred without maternal toxicity.

As significant developmental effects are observed that cannot be considered secondary to maternal toxicity, classification for reproductive toxicity is justified. Classification in Category 1A should be largely based on evidence in humans. No studies in humans are available, thus classification in Category 1A is not appropriate.

Depending on the reliability of the studies and the relevance of the effect, classification in either Category 1B or 2 may be proposed. There is no information available indicating or showing that the observed effects are not relevant to humans.Considering the severity and dose-dependency of the effects and their occurrence at low doses that induced no or only minor maternal toxicity, classification in Category 1B is considered more appropriate than Category 2. For these reasons, classification in Category 1B is proposed for developmental toxicity.

Most developmental effects were observed at 30 and 90 mg/kg bw/day indicating an ED10 within the range of 4 and 400 mg/kg bw/day. The eye lens effects were also observed at 10 mg/kg bw/day with an incidence of 6%. Therefore, the ED10 is also expected to be in this range. Therefore, no SCL is required.

10.10.7 Adverse effects on or via lactation

No data available

10.10.8 Conclusion on classification and labelling for reproductive toxicity

Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. needs to be classified as Reproductive toxicant Category 1B H360D according to Regulation (EC) 1272/2008.

RAC evaluation of reproductive toxicity
Summary of the Dossier Submitter's (DS) proposal *Fertility and sexual function* No one- or two-generation reproductive toxicity study was available for Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. Only 90-day oral repeated dose toxicity studies that were available were in rat and dog; these were compliant with OECD TG 408 and 409, respectively, and with GLP. In both these studies, no adverse effects were recorded at the macroscopic and microscopic examination of the male and female reproductive organs. Although no relevant effects on reproductive organs were seen in 90d repeated dose studies, the DS proposed no classification for effects on sexual function and fertility due to the absence of one- or two-generation reproductive studies, in which effects on sexual performance and fertility are usually examined. *Development* One oral (gavage) prenatal developmental toxicity study (OECD TG 414, GLP compliant) was available. In this study, 22 pregnant Wistar rats were exposed to the test substance at doses of 0, 10, 30, and 90 mg/kg bw/day from day 6 to day 20 post coitum (p.c.) and scheduled C-section was performed on day 21 p.c. Several adverse effects on embryofetal development including post-implantation loss, external abnormalities of the head, altered texture of the cut surface of the eye lens as well as abnormalities of cervical vertebrae and of cranial bones, were recorded at 90 mg/kg bw/day. The abnormalities of cervical vertebrae were also recorded at 30 mg/kg and the effect on the eye lens was observed as well at both 30 and 10 mg/kg bw/day (see Table 2 for more details). The altered texture of the cut surface of the eye lens was considered by the DS to be treatment related and severe because of a clear dose-response relationship and because microscopically identifiable cataracts were observed at a high incidence (18/39) in the rat 90-day repeated dose toxicity study at the high dose level (150 mg/kg bw/day) (see Annex I to the Background Document for further details). The DS concluded that the LOAEL for the lens effect in the prenatal developmental toxicity study was lower than the LOAEL for cataracts in adult animals, which indicates that developing animals may be more susceptible to this effect. The DS considered that the reduced body weight gain that was recorded at C-section at the highest dose level (+30±11% statistically significant compared to +44±6% in the control group, when calculated as percentage of weight on day 6 p.c.), most likely was largely secondary to the post-implantation loss (30%, statistically

significant) and the reduced body weight of the pups (-4% as compared to the controls). Consequently, the mean corrected body weight gain (when calculated as percentage of weight on day 6 p.c.) was similar for the high dose group (+6.6±7.3) and the controls (+10.7±5.0%). The DS also highlighted that a small decrease in body weight gain does not normally result in an increase in post-implantation loss or in other developmental effects as even an absolute reduction in body weight due to feed restriction did not result in an increase in post-implantation loss (Fleeman, 2005).

According to the DS there was no information available indicating or showing that the observed effects would not be relevant for humans. In view of the severity and dose-dependence of the recorded effects on foetal development and their occurrence at low doses that induced no or only minor maternal toxicity, the DS considers that classification in Category 1B would be more appropriate than classification in Category 2.

Effects on or via lactation

The DS stated that no data was available and therefore this endpoint could not be assessed.

Specific concentration limit (SCL)

According to the DS, no SCL is required. At the lowest LOAEL (i.e. 10 mg/kg bw/day) an incidence of 6% for the effect on the eye lens was recorded. Consequently the ED_{10}-value for this effect is not expected to be within the range for the high potency group (ED_{10}<4 mg/kg) for which an SCL is applied (see Table 3.7.2-e in the Guidance on the Application of the CLP Criteria).

Comments received during public consultation

Five comments were received during the public consultation.

The four MSCA who commented were all in support of the proposed classificationas Repr. 1B-H360D. One MSCA requested information on an individual level for body weight gain and post-implantation losses in order to examine if the recorded post-implantation loss was linked to effects on body weight gain. This MSCA also asked for historical control data for the cleft lip malformation. One MSCA had noted that irritation of the stomach was reported from 30 mg/kg bw/day in the 90-day repeated dose toxicity study in the rat and was surprised that no similar effect was recorded in the prenatal developmental toxicity study. The DS confirmed that there was no reporting of an effect on the stomach and clarified that the absence of reported stomach irritation may be due to the limitations in the examination of the dams (in this study type, internal organs are only examined macroscopically). The DS also proposed that the recorded differences could possibly be linked to the shorter exposure time (15 days, as compared to 90 day in the repeated dose toxicity study) or to the use of different solvents in the two studies (water in the 90-day study and PEG-300 in the developmental toxicity study).

Assessment and comparison with the classification criteria

Fertility and sexual function

No one- or two-generation studies were available.

No effects were recorded at the macroscopic and microscopic examination of the reproductive organs (ovaries, testes with epididymides, uterus with vagina and cervix, mammary gland and prostate) in the oral rat 90-day repeated dose toxicity study or in the oral dog 90-day repeated dose toxicity study at dose levels up to and including 150 and 100 mg/kg bw/day, respectively.

The RAC notes that since no sexual function and fertility studies were submitted, the available data do not allow for an assessment of whether e.g. mating behaviour or sexual maturation would have been affected and therefore whether Ethanol, 2,2'- iminobis-, N-(C13-15-branched and linear alkyl) derivs. would adversely affect sexual function and fertility. In conclusion, the RAC agrees with the DS that, due to lack of data, no classification for effects on sexual function and fertility is warranted.

Development

One oral gavage prenatal developmental toxicity study (OECD TG 414, GLP compliant) is available. In this study, 22 pregnant rats were exposed to the test substance at doses of 0, 10, 30, and 90 mg/kg bw/day from day 6 to day 20 p.c. No pre-terminal deaths or adverse clinical findings were noted and no adverse findings were found at the gross macroscopic examination of the dams at the end of the study. A lower food intake was seen in the high dose dams (10-12% less as compared to controls, statistically significant from days 12-15 p.c. until the end of study) and the absolute body weight was statistically significantly lower than the controls from day 19 p.c. until scheduled C-section on day 21 p.c. (See the Table below and the CLH report for further information).

Table. Maternal effects (modified from Table 1, Annex I to the CLH report)

	Vehicle	10 mg/kg bw/day	30 mg/kg bw/day	90 mg/kg bw/day
Food consumption				
Day 6-9 p.c.	21.2 ± 2.8	21.0 ± 2.2	20.5 ± 2.0	19.7 ± 2.1
Day 9-12 p.c.[1]	22.4 ± 2.6	22.0 ± 2.0	21.4 ± 2.1	20.8 ± 2.0 [-7%]
Day 12-15 p.c.[1]	23.3 ± 2.3	23.1 ± 2.5	23.0 ± 1.9	20.9 ± 3.2** [-10%]
Day 15-18 p.c.[1]	25.1 ± 2.9	24.5 ± 2.3	24.0 ± 2.4	22.7 ± 1.9 ** [-10%]
Day 18-21 p.c.[1]	24.5 ± 3.2	23.5 ±3.3	23.6 ± 3.1	21.5 ± 4.5* [-12%]
Maternal body weights				
Day 0 p.c	238 ± 10	234 ± 9	236 ± 10	243 ± 11
Day 6 p.c.	255 ± 10	250 ± 9	254 ± 11	263 ± 13
Day 13 p.c.	283 ± 11	278 ± 12	281 ± 12	284 ± 13
Day 18 p.c.	329 ± 16	326 ± 15	325 ± 15	318 ± 17
Day 19 p.c	342 ± 16	339 ± 16	337 ± 17	325 ± 19**

Day 21 p.c.[1]	367 ± 20	364 ± 20	361 ± 20	342 ± 24** [- 7 %]
Body weight gain, days 6 – 21 p.c. (g)[1,2]	112	114	107	79 [-30%]
- Calculated as % of weight on day 6 p.c.	44 ± 6	46 ± 5	42 ± 8	30 ± 11**
Gravid uterus weight (g)[1]	84.4 ± 12.2	89.3 ±8.0	81.7 ± 20.0	62.6 ± 24.3 [-26%]
Corrected body weight day 21 p.c. (g)[1,2]	282.6	274.7	279.3	279.4 [-1%]
Corrected body weight gain, days 6-21 p.c. (g)[1]	27.2 ±12.3	25.6 ± 10.8	25.2 ± 15.0	16.9 ± 18.8 [-38%]
- Calculated as % of weight on day 6 p.c.	10.7±5.0	10.2±4.3	10.0±6.0	6.6±7.3

1) The number in brackets represents the decrease or increase as compared to the controls; 2) Calculated by RAC, from data as presented in this table, no statistical analysis performed. */** Dunnett-test, statistically significant at 5% (*) or 1% (**).

The developmental toxicity was manifested as follows:

1. A significant increase in post-implantation losses was noted for the high dose dams (30.2%, statistically significant as compared to 2.6% in the controls). This was caused by an increase in the number of embryonic resorptions (mean per dam: 4.0 ± 4.5, statistically significant as compared to 0.3 ± 0.5 in the controls; historical control data (HCD): range, 1.0-1.5, median 1.1) and losses were recorded in 13/20 dams in the high dose group as compared to seven dams in the controls. Consequently the mean gravid uterus weight (-26% as compared to controls, not statistically significant) as well as the mean viable litter size (9.3±4.0 foetuses, statistically significant as compared to 12.6±2.0 in the controls) were also decreased in the high dose group. During public consultation, one MSCA requested individual data for post-implantation loss, maternal body weight and corrected body weight gain to clarify to what extent the recorded post-implantation loss in the high dose group was linked to the observed maternal toxicity (i.e. a reduced mean corrected body weight gain (Days 6 – 21 p.c.: 16.9±18.8 as compared to 27.2±12.3 g in the controls)). This data was provided for the high dose group and the control (see DS response to comment #5 in the RCOM document in Annex 2 for further details).

Based on this data, RAC concurs with the DS that on an individual level there was no correlation between post-implantation loss and a reduced corrected body weight gain (i.e. no embryonic resorptions were recorded in the three dams with the lowest corrected body weight gain). Consequently, the increase in post-implantation loss should not be viewed as being a nonspecific secondary consequence of the maternal toxicity recorded in this study. This conclusion is also supported by studies that examined the effects of feed restriction on foetal development in rats (Fleeman et al., 2005; Carney et al., 2004).

2. A dose dependent increase in the incidence of cervical vertebra abnormalities was noted at the intermediate and high dose levels (0, 1 (1), 3(3) and 7(7) foetuses (litters) in

the control, low, intermediate and high dose groups, respectively). In addition an increased incidence of external abnormalities of the head (5 foetuses from 4 litters), as well as an increase in the number of foetuses with cranial bone abnormalities (5 foetuses from 5 litters) was observed in the high dose group (see Table 2 and the Background Document for further information). RAC notes that not only the DS but also in the original study report it was concluded that the cervical vertebra abnormalities as well as the cranial bone abnormalities were related to the substance. RAC concurs with this analysis. RAC also notes that the recorded external abnormalities "missing eyes" and "cleft lip", that each were observed in 2 foetuses (from 2 litters), are rare findings since there was no recording of foetuses with anopthalmia, microopthalmia, "eyes reduced in size/small" or with cleft/misshapen/absent palates in the available HCD. In addition, an additional high dose foetus also had abnormal eye (" eye small severe") that was only revealed by the visceral examination. Therefore, in total there were 3 foetuses (from 3 litters) with abnormalities of the eyes.

At the visceral examination, alterations of the texture of the cut surface of the eye lens was observed. This finding is normally claimed to be a process artefact. However, RAC notes the clear dose-response relationship (0 foetuses (0 litters), 9(6), 31(15), 58(19) in the control, low, intermediate and high dose levels, respectively) as well as the absence of this finding in the concurrent control and in the provided HCD. The authors of the study report also acknowledged the possibility of a link between the test item and the effect on the eye lens. The registrant claimed that the observed effect on the eye lens still could be a process artefact since the eyes were examined by dose group, and since the lowest group was processd first it was less affected by the storage fluid (see CLH report, section 10.10. 5). However there is no information in the study report that supports this claim and no further justification (i.e. information or data) has been provided during the CLH process to substantiate this claim. Therefore, RAC concludes that the observed dose-response relationship still indicates that the finding is substance related rather than a process artefact. Microscopically identifiable cataracts were recorded at a high incidence (18/39) in the rat (but not in the dog) 90-day repeated dose toxicity study at 150 mg/kg bw/day. The effect on the eye lens of foetuses was recorded at a lower dose level (i.e. 10 mg/kg bw/day), suggesting that the developing eye lens might be more susceptible than the adult eye lens to effects of Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. RAC therefore considers that this increases the concern that the finding of an alteration of the texture of the cut surface of the eye lens in foetuses exposed *in utero* to Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. is treatment-related.

Table. Main abnormalities recorded at the foetal pathology examination (modified from Tables 3-5 , Annex I to the CLH report)

Observations[1]	Vehicle	10 mg/kg bw/day	30 mg/kg bw/day	90 mg/kg bw/day	HCD[2]
External **Abnormalities** and variations[3]					
Number of foetuses (litters) examined)	264 (21)	300 (22)	249 (20)	185 (20)	1573 (129)
Number of foetuses (litters) with abnormalities	0	1	0	5 (4)	0-1
Lower jaw shortened, mouth closed		1			No information is available for

Head slightly misshapen				1	external findings. Data below refer to incidences in the visceral HCD. No cleft/misshapen or absent palates. No Anopthalmia, microphalmia or "eyes reduced in size/small".
No skin over head, clear membrane covering brain, **nasal opening missing, eyes missing, cleft lip**				1	
Eyes missing, clear membrane over part of brain				1	
Cleft lip right				1[4]	
Lower jaw slightly shortened, hematoma on lower jaw, cyst-like structure on genital region				1[4]	
Visceral examination					
Number of foetuses (litters) examined	137 (21)	153 (22)	133 (20)	97(20)	817 (129)
Number of foetuses (litters) with abnormalities[5]	1	1	0	2(2)	No data
Eye lens cut surface altered texture (assumed to be a probable process artefact by registrant)	0	9(6)	31(15)	58(19)	0
Skeletal (bone and cartilage) examination					
Number of foetuses (litters) examined	127(21)	147(22)	116 (20)	87 (20)	755 (129)
Number of foetuses (litters) with abnormalities	1(1)	2(2)	3(3)	8(8)	No data
Cervical vertebra abnormalities[6]	0	1(1))	3(3)	7(7)	No information is available for these two compiled observations.
Cranial bone abnormalities[7]	1	1	1	5(5)	

1) The study report (including the HCD), which was made available to RAC, only distinguish between abnormalities and variations and use the following definitions: "*Abnormalities*, a structural change in a fetus that would probably impair its health or development. *Variation*, A fetal change that is unlikely to adversely affect survival or health. This includes a delay in growth or morphogenesis that has otherwise followed a normal pattern of development." 2) The HCD consists of 6 studies performed 2010; the concurrent study was performed in 2013. Consequently, the available HCD needs to be handled with caution. However RAC still finds the HCD to be somewhat useful since it gives some information on the frequencies of the findings in the same strain of rats at the test facility where the concurrent study was performed. 3) The heading indicates that the description of the listed findings includes abnormalities as well as variants. Neither the CLH report nor the original study report contains any information that clarifies which findings are variants and which are abnormalities. Based on how abnormalities and variants are defined in the study report, findings that RAC presumes to be abnormalities are indicated in bold. 4) Littermates. 5) Control: bilateral dilation of lateral ventricle of the brain. Low dose: situs in versus. High dose: one foetus with bilateral dilation of the lateral ventricle of the brain with a severely small eye (NB, this was not one of the foetuses with "missing eyes") and another foetus (from a different litter) with anal atresia. 6) Cervical vertebra ventral arch, body or dorsal arch absent, fused (to odontoid process or other vertebral structure), misshapen, interrupted, short and/or split. 7) Absent, fused and/or misshapen skull bone(s); cleft or misshapen palate, hyoid arch structure absent or duplicated.

At the skeletal examination, statistically significantly increased foetal incidences (with low

magnitude but commonly outside the available HCD) of the following variants were recorded in the high dose group (see Table below):

- Foetuses with effects on the degree of ossification of a number of skull bones (occipital, parietal, interparietal and frontal)
- Foetuses with a long ventral plate (cartilaginous cervical vertebrae)
- Foetuses with supernumerary rudimentary ribs
- Foetuses with wavy ribs

At the visceral examination a somewhat higher incidence (and outside available HCD) of malpositioned testis (a variant) was also observed in the high dose group (see Table below).

RAC considers that it is of limited or no value to conclude whether the increased incidence of these variants are primary or secondary to maternal toxicity. The severe effects on foetal viability and increased incidence of several abnormalities are considered sufficiently clear evidence to justify classification.

Table. Main skeletal and soft tissue variations (modified from Tables 4 and 5, Annex I to the CLH report).

Foetal (litter) incidence[1]	Control	10 mg/kg bw/day	30 mg/kg bw/day	90 mg/kg bw/day	HCD: range foetus(litters)
Incompletely ossified Os occipitale	1 [5%] (1)	3 [2%] (3)	2 [2%] (2)	6 [7%]** (6) [30%]*	1(1) – 4(3)
Incompletely ossified Os parietal, bilateral	2 [2%] (2)	4 [2%] (3)	8 [7%]* (6)	16 [18%]** (9) [45%]*	0(0)-5(4)
Incompletely ossified Os interparietale	1 [1%] (1)	7 [5%] (6)	5 [4%] (4)	10 [11%**] (8) [40%]**	1(1)-10(7)
Incompletely ossified Os frontale, left	2 [2%] (2)	3 [2%] (3)	5 [4%] (4)	10 [11%]** (8) [40%]*	0(0)-4(3)
Incompletely ossified Os frontale, right	2 [2%] (2)	3 [2%] (3)	5 [4%] (4)	10 [11%]** (8) [40%]*	0(0)-4(3)
Rib, wavy	0	3(3)	0	8(7)	No data
Supernumerary rib, one rudimentary rib(s), - left	8 [6%] (5)	24 [16%]** (8)	12 [10%] (8)	21 [24%]** (13) [65%]**	17 -29 (10-14)
- right	7 [6%] (5)	22 [15%]** (9)	10 [9] (7)	17 [20%]** (11) [55%]*	11-21 (7-12)
Cartilaginous cervical vertebrae, long ventral plate, - left	0 [0] 0	2 [1] (2)	1 [1] (1)	6 [7%]** (5) [25%]*	0(0)- 1(1)
- right	1[1%] (1)	1[1%] (1)	3 [3%] (3)	8 [9%]** (6) [30%]*	0(0) – 1(1)
Testis malpositioned	1(1)	4(3)	2(2)	6(6)	0-3 (0-2)

[1]Incidences are presented as total number of affected foetuses (litters); numbers in brackets represents % of foetuses in a group or % of litters in a group. Statistical analysis (Fischer's exact test significant at level 5% (*) or 1% (**)) was only performed on the relative incidences.

Conclusion regarding classification for adverse effect on development

Since there is no evidence that Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. adversely affects foetal development in humans, Category 1A is not justified.

RAC agrees with the DS that classification in Category 1B is justified based on *clear* evidence from a reliable prenatal developmental toxicity study in rat of adverse effects on foetal development. The effects on development (embryonic mortality, abnormalities of the cervical vertebrae and the cranial bones, effects on the eyes as well as the increased incidence of an altered texture of the cut surface of the eye lens) are not considered to be secondary non-specific consequences of the othertoxic effects (effects on food consumption and maternal body weight) that were noted in the high dose group. RAC also notes that the cervical vertebra abnormalities and the recording of an altered texture of the cut surface of the eye lens were observed at dose levels where no maternal toxicity was recorded.

In agreement with the DS proposal RAC concludes that classification as Rep. 1B; H360D is justified.

Setting of an specific concentration limit (SCL)

RAC concurs with the argumentation of the DS for why an SCL for adverse effects on development is not needed.

Effects on or via lactation

There is no data available and therefore this endpoint cannot be assessed.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Table 10: Summary table of relevant repeated dose toxicity studies

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Repeated Dose 90-Day Oral Toxicity (OECD 408), rats, Sprague Dawley, 20 sex/dose	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs., 15, 30 and 150 mg/kg bw/day, Duration of exposure: 13	NOAEL: 15 mg/kg bw/day (nominal) (male/female) High dose effects include: mortality (5/40), salivation, wheezing, weight loss, urine stains, alopecia, ocular opacity, cataract (18/39), gross findings in the nonglandular stomach (38/40) Mid dose effects include: mortality (2/40), gross findings in the nonglandular stomach (4/40)	Exp Key Repeated dose toxicity: oral.003

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	weeks, 7 days/week		
Repeated Dose 90-Day Oral Toxicity in Non-Rodents (OECD 409), dog, Beagle, 4 sex/dose	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs., 15, 30 and 100 mg/kg bw/day, Duration of exposure: 13 weeks, 7 days/week	NOAEL: 30 mg/kg bw/day (nominal) (male/female) High dose effects: increased incidence of salivation, emesis, and/or soft feces, increased mean alanine aminotransferase value in females, tissue alterations in the liver of females	Exp key rep dose tox: oral.002

10.13 Non-human information

10.13.1 Repeated dose toxicity: oral

Although repeated dose toxicity was not assessed for classification in this report, the 90-day study in rats and the 90-day study in dogs are provided as they give more insight in the toxic mechanism of the substance and the occurrence of maternal toxicity.

A 90 day repeated oral dose toxicity study was performed according to OECD guideline 408 with male and female Sprague Dawley rats (Exp Key Repeated dose toxicity: oral.002). 20 animals per sex and dose were treated using gavage (vehicle water) with 0, 15, 30 and 150 mg/kg bw for 13 weeks.
In the high dose group, five animals were found dead during the study period. All animals in the 150 mg/kg/day group exhibited salivation and wheezing. These signs were first noted during week 2 and persisted throughout the duration of the treatment period. Other clinical signs noted primarily in this group included thinness, urine stains, alopecia, rough hair coat, and red area on the face, ear, neck, leg(s), mouth, chest, and/or paw(s). Body weights for the 150 mg/kg/day males were generally lower than control values and corresponded with lower food consumption values for this group. Furthermore haematological findings, changes in serum chemistry parameters and mean absolute organ weights and/or organ-to-terminal-body-weight ratios and gross findings were made in the 150 mg/kg bw group. Most changes were considered secondary to local stomach irritation and inflammatory lung lesions. The lung lesions occurred in 10/40 animals and were attributed to incidental aspiration of the test material. Stomach lesions (acanthosis) were observed in 38/40 animals.
As a systemic effect, notable ophthalmoscopic findings were reported, including posterior subcapsular or complete cataracts observed in-life in 21 high-dose animals. Microscopically, the incidence of cataracts was noted to be 18/39 animals in the 150 mg/kg bw/day group.

In the mid-dose group, gross findings in the nonglandular stomach were noted in 4/40 animals and two animals were found dead. Inflammatory lung lesions were noted for 2/40 animals in this group.

Notable ophthalmoscopic findings were reported for two animals in the mid-dose group in-life, but there were no microscopically identifiable cataracts in these mid-dose animals.

A 90-day study was performed in which the test material was administered via capsule to three groups of dogs (four dogs/sex/group) at dose levels of 15 (Group 2), 30 (Group 3), or 100 (Group 4) mg/kg/day. A control group of four dogs/sex (Group 1) received an empty capsule daily.
All dogs were observed twice daily for mortality and moribundity and once daily (approximately 2 to 3 hours post dose) for obvious indications of a toxic and/or pharmacologic effect. Individual body weights were recorded prior to initiation of dosing and weekly thereafter. Individual food consumption measurements and physical examinations were performed weekly. Indirect ophthalmoscopic examinations were performed on all dogs prior to initiation of dosing and on control and high-dose dogs prior to termination. Clinical pathology parameters (hematology and blood chemistry) were evaluated at termination. Following at least 13 weeks of administration of the test material, all dogs were humanely sacrificed and subjected to a complete gross necropsy. Organ weight evaluations and a histomorphologic examination of protocol-specified tissues were performed, including testes with epididymides and uterus with vagina and cervix.
All dogs survived to the scheduled termination of the study. Clinical observations, apparently related to administration of the test material, included an increased incidence of salivation, emesis, and/or soft feces (mucoid only or mucoid/bilious) in the Group 4 males and/or females. Statistical evaluation of mean body weight, mean body weight gain, and mean food consumption values failed to demonstrate any significant differences when treated groups were compared to respective control values. The ophthalmoscopic observation noted unilateral lateral mucoid lacrimation in the eye of one high dose female, but this finding was considered incidental.
Statistical evaluation of clinical pathology values revealed a significantly elevated mean erythrocyte value and a mean alanine aminotransferase value in the Group 4 females and a significantly elevated mean calcium value in the Group 3 and 4 females. In addition, the Group 3 male mean blood urea nitrogen value was significantly depressed as compared to the control value. Based on the small magnitude of change, absence of a dose response, or unusually low mean control value, the changes in calcium, blood urea nitrogen, and erythrocyte values, respectively, are felt to be incidental to treatment.
There were no apparent compound-related gross necropsy observations noted at termination. In addition, statistical evaluation of mean absolute and relative organ weight data failed to reveal any significant differences when treated groups were compared to the respective mean control values. Histomorphologic examination of tissue sections revealed apparent compound-related changes in the livers of the Group 4 females, comprised of increased pigment accumulation noted in the Kupffer cells and bile canaliculi. No histopathological changes of the eye were reported.
Based on the data generated from this study, the no-observable-effect level of the substance when administered via capsule for approximately 13 weeks to male and female beagle dogs is 30 mg/kg/day.

10.14 Aspiration hazard

Not evaluated in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier.

13 ADDITIONAL LABELLING

Not evaluated in this dossier.

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15 ANNEXES

Annex I to the CLH report