Committee for Risk Assessment

RAC

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

Adopted

22 September 2017

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22 September 2017

CLH-O-0000001412-86-166/F

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

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

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

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

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

The proposal was submitted by the **Netherlands** and received by RAC on **19 October 2016.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **21 November 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **16 January 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anne-Lee Gustafson**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **22 September 2017** by **consensus**.

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

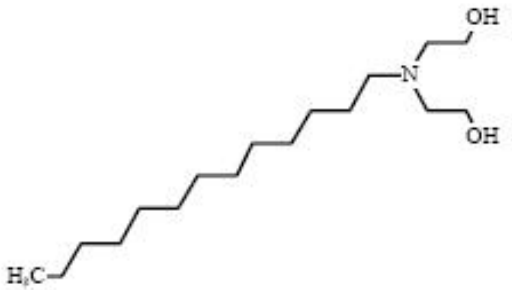
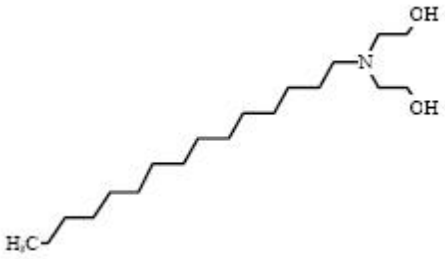
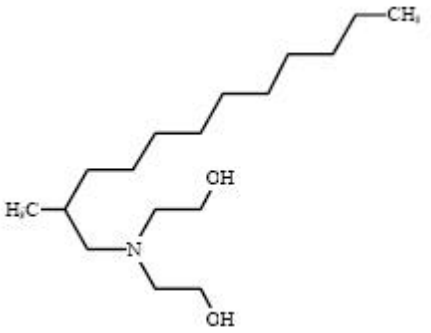
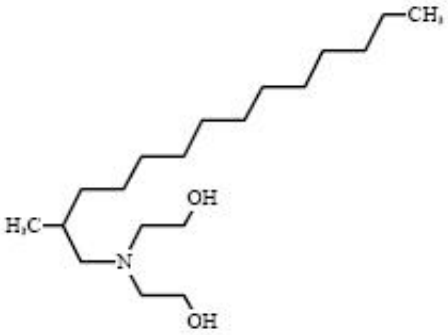
	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	xxx-xxx-xx-x	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.	308-208-6	97925-95-6	Repr. 1B, H360D	H360D	GHS08 Dgr	H360D	-	-	-
RAC opinion	xxx-xxx-xx-x	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.	308-208-6	97925-95-6	Repr. 1B, H360D	H360D	GHS08 Dgr	H360D	-	-	-
Resulting Annex VI entry if agreed by COM	xxx-xxx-xx-x	Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.	308-208-6	97925-95-6	Repr. 1B, H360D	H360D	GHS08 Dgr	H360D	-	-	-

GROUNDS FOR ADOPTION OF THE OPINION

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.

HUMAN HEALTH HAZARD EVALUATION

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 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".
Head slightly misshapen				1	
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 distinguishes 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 - right	8 [6%] (5) 7 [6%] (5)	24 [16%]** (8) 22 [15%]** (9)	12 [10%] (8) 10 [9] (7)	21 [24%]** (13) [65%]** 17 [20%]** (11) [55%]*	17 -29 (10-14) 11-21 (7-12)
Cartilaginous cervical vertebrae, long ventral plate, - left - right	0 [0] 0 1[1%] (1)	2 [1] (2) 1[1%] (1)	1 [1] (1) 3 [3%] (3)	6 [7%]** (5) [25%]* 8 [9%]** (6) [30%]*	0(0)- 1(1) 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.

Additional references

Carney E.W., Zablotny C.L., Marty M.S., Crissman J.W., Anderson P., Woolhiser M., Holsapple M. (2004). The effects of feed restriction during in utero and postnatal development in rats. Toxicol. Sci. Nov;82(1):237-49.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).