Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM) 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

Adopted
22 September 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ETHANOL, 2,2'-IMINOBIS-, N-(C13-15-BRANCHED AND LINEAR ALKYL) DERIVS.

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs.
EC number: 308-208-6
CAS number: 97925-95-6
Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.01.2017	Sweden		MemberState	1
Comment received				
The Swedish CA considers that Annex I contain information which preferably should have been included in the public consultation, such as data on all observed critical effects, statistical analysis and route of administration. It is not stated in the report or in the Annex that the Annex is confidential. To assure a transparent process for public consultation, we believe that detailed information that is not confidential should be transferred to an Annex which is publicly available. Naturally, confidential information should be included in a confidential Annex, which can only be access by agreed parties, e.g. Member State Competent Authorities, ECHA, the Commission and lead registrant.				
Dossier Submitter's Response				
Thank you for your comment. The latest revision (01-12-2015) of the CLH report template was used for this CLH report. In this version, only the study summaries and hazard assessment are included in the report, while all the detailed study summaries of the studies forming the basis of the CLH proposal are provided in Annex I. This Annex was not intended as a confidential annex.				
ECHA				
Due to a technical problem, Annex I to the CLH report containing detailed study summaries of the studies forming the basis of the CLH proposal was not available during the public consultation. However, an additional public consultation of the CLH report and Annex I was subsequently launched between 4-24 April 2017.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2017	United Kingdom	<confidential>	Company-Manufacturer	2
Comment received				
registering so kept informed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2017	Germany		MemberState	3
Comment received				
The German CA agrees with the proposed classification of Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. as Repr. 1B, H360D.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC notes the support for the proposed classification in Repr. 1B – H360D.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
04.01.2017	France		MemberState	4
Comment received				
☐ page 10 Could you please clarify if the reported "abnormalities" in table 9 can be classified as malformations? Since irritation of stomach is reported in the 90-day study from 30 mg/kg bw/day, it is surprising that such effects are not observed in the prenatal developmental study at doses up to 90 mg/kg bw/d. Could you please confirm the lack of effects on the stomach in the prenatal study? Overall, we agree with the proposed classification.				
Dossier Submitter's Response				
Thank you for your comments and your support. The abnormalities reported in table 9 can indeed be classified as malformations. They include slightly misshapen head, no skin over head, missing eyes and nasal opening, cleft lip and clear membrane over part of head, as well as absent, fused and/or misshapen skull cranial bones and/or cervical vertebra. Although all fetuses were not affected by the same abnormality, a possible association to treatment could not be ruled out. There is no mention of effects on the stomach in the study report of the prenatal study. However, only macroscopic examination of the internal organs was performed. Therefore, the absence of reported stomach irritation may be due to the limitations in the examination of the dams. There is also a possibility that the difference is linked to the				

shorter exposure time of the PNDT (15 days), compared to the 90-day study. A third explanation could be the difference in vehicle. Both studies used gavage exposure. However, in the prenatal study PEG-300 was used whereas water was used in the 90-day study.
RAC's response
RAC notes the support for the proposed classification (Repr. 1B – H360D).

Date	Country	Organisation	Type of Organisation	Comment number
16.01.2017	Sweden		MemberState	5
Comment received				
The Swedish CA supports classification of Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs. (CAS No. 97925-95-6) in Repr. 1B H360D as specified in the proposal. However, we would welcome some clarifications concerning maternal toxicity and we would also like to get some additional data. Page 11 regarding the maternal body weight gain. We believe it is important to analyse the effects on the maternal body weight gain. However, it is difficult to assess the effects as the data is presently presented. We are of the opinion that the maternal body weight gain should be presented in a different way. Please compare the maternal body weight gain by setting the control group to 100%, as this is a more common and accepted practice for comparing changes in maternal body weight. In addition, please compare the maternal body weight change as stated in section 3.7.2.4.4 in the CLP criteria, by calculating an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses). This may indicate whether the effect is maternal or intrauterine. The relevance of the statistically significant reduced mean body weight gain in the high dose group on day 4 and days 7 to 8 post coitum (p.c.) can be questioned, since the dosing started on day 6 p.c. Page 12 in CLH report and page 10 and 11 in Annex I regarding maternal toxicity. Regarding the corrected weight gain of the dams, (16.9 g ± 18.8 in high dose group (90 mg/kg bw/day) compared to 27.2 g ± 12.3 in control group), we believe that it is indicating a 38% reduction in body weight gain, however not statistically significant. In the Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment, Number 43, para 58, it is referred to two feed restriction studies in the rat and rabbit (Fleeman, 2005 and Cappon, 2005) which clearly showed that severe weight loss or decrease in body weight gain per see induced minor changes in skeleton development but no effects on viability or malformations in the rat. Moreover, the mean total weights (g) of live fetuses, although statistically significant for mid- and high dose (30 and 90 mg/kg bw/day), should only be considered as a minor effect. In addition, the severe developmental effects observed at 30 mg/kg bw/day occurred without maternal toxicity. Regarding general toxicity of the dams, we note a repeated dose 14 days dose finding study on rats in the REACH Registration, Study report 1991, (reliable with restrictions) where the doses (30, 100 and 300 mg/kg bw/day) and the exposure period (14 days) seems relevant in comparison to the pre-natal developmental toxicity study. In the 14 days study, body weight change and food intake were significantly depressed for 300 mg/kg bw/day group males, with a nonsignificant depression in body weight change for the 100 mg/kg bw day group males and 100 mg/kg bw/day and 300 mg/kg bw/day group females. Histopathology examination of the liver and kidneys from the control and high-dose groups revealed no treatment-related alterations. In conclusion, we agree that the sever fetotoxic effects are unlikely secondary non-specific effects, since they occur with a				

dose dependency and at doses were maternal toxicity is not evident.

Page 11 in Annex I regarding post-implantation loss in relation to fetuses
It is noted that there is a statistically significant increase of post-implantation loss and a statistically significant decrease in mean total number of fetuses per dam in the high dose group, while there is no total intrauterine death for any dam. We would like to know if the post-implantation loss is more common in dams displaying prominent maternal toxicity. If available, please specify the number of post-implantation loss per dam together with body weight gain in gram for each dam in the high dose group and in the control group.

We would like to know if there is any additional reproductive toxicity data available on any of the four constituents making up this substance. In addition, we would like to know if there are any indications that any of the constituents can cause severe eye effects such as altered texture of the cut surface of the eye lens.

Page 12 in Annex I, table 3, regarding cleft lip in fetuses
At high dose, two fetuses are found with cleft lip. We believe that this is a major malformation. In the text on page 7 it is stated that the abnormal findings during the external examination was noted in 5 fetuses in 4 litters. Is the cleft lip malformation observed in the same litter? Are there historical control data for this effect for comparison?

Page 11-12 in the CLH report and page 13 in Annex I regarding altered texture of the cut surface of the eye lens.
We support DS in their conclusion that the altered texture of the cut surface of the eye lens should be considered an adverse treatment related effect, because of the clear dose effect relation. In addition, no such eye effects were observed in the historical control data, comprising 6 embryofetal developmental studies performed at the testing laboratory throughout the year 2010. It is stated that the study is performed according to GLP, so there should be Standard Operation Procedures for this type of examination, making sure that it is not an artefact of poor procedures. Moreover, eye lens defects were observed in the 90 day repeated dose toxicity study on rat, as stated on page 14. Notable ophthalmoscopic findings were reported, including posterior subcapsular or complete cataracts observed in-life in 21 animals at 150 mg/kg bw/day. Microscopically, the incidence of cataracts was noted to be 18/39 animals at 150 mg/kg bw/day. At 30 mg/kg bw/day, notable ophthalmoscopic findings were reported for two animals in-life, but there were no microscopically identifiable cataracts in these mid-dose animals.

Page 8 in Annex I
Is there text missing in the last sentence?

Overall assessment of reproductive toxicity
The Swedish CA agrees with DS conclusion that several dose-related and severe fetotoxic effects were reported in a prenatal development study in rats, including post-implantation loss, external abnormalities of the head, altered texture of the cut surface of the eye lens, cervical vertebrae and cranial bone abnormalities at the highest dose. Altered texture of the cut surface of the eye lens and cervical vertebrae abnormalities were noted in mid and low dose groups (30 and 10 mg/kg bw/day) in a dose dependent manner, without maternal toxicity, which strengthens the relevance of the effects. Considering the severity and dose-dependency of the effects and their occurrence in low doses that induced no or only minor maternal toxicity, it does not seem likely to be secondary non-specific effects. Hence, classification in Category 1B is considered appropriate for developmental toxicity.

Dossier Submitter's Response

Thank you for your comments and your support.

Page 11 regarding the maternal body weight gain. The mean maternal body weight gain between day 6 and day 21 was 112 gr for the control and 79 gr in the high dose group, which is a reduction of 29.5%. The body weight gains at the low/mid dose groups were +2% and -4.5% compared to the controls.
The corrected mean body weight gain was 27.2 gr in the control group and 16.9 gr at the high dose, which is indeed a reduction of 37.9%. The corrected body weight gain at the mid dose (30 mg/kg) was 7.4% lower and the low dose (10 mg/kg) 5.9% lower compared to the control.

In the following tables, the individual data for post-implantation loss, body weight of the dams, and the corrected body weight gain are given for the control and high dose groups. The data do not indicate that the increase in post-implantation loss (embryonic death) is related to a reduction in corrected bodyweight gain.

Control group

FEMALE		CORP. LUTEA	IMPL.	EMBRYONIC DEATHS	LIVE FETUSES	BW D6	BW D21	CORR. BW GAIN (GR)
1		14	14	0	14	255	378	27,3
2		12	12	0	12	233	351	40,2
3		14	13	0	13	254	374	35,4
4		12	12	0	12	242	332	17,9
5	<RE>	6	1	1		241	255	0,0
6		13	13	0	13	247	379	51,0
7		10	10	0	10	247	350	32,7
8		13	13	0	13	252	391	43,3
9		13	11	0	11	242	354	31,8
10		12	12	2	10	256	360	30,9
11		14	14	0	14	260	385	31,6
12		15	15	0	15	266	387	19,8
13		12	12	0	12	261	386	43,4
14		14	14	1	13	259	372	24,8
15		15	15	0	15	280	388	8,9
16		13	12	1	11	250	342	16,7
17		10	10	1	9	254	356	32,9
18		13	13	0	13	254	346	9,0
19		18	17	1	16	263	375	6,3
20		14	13	1	12	255	353	26,2
21		16	16	0	16	271	403	27,6
22		10	10	0	10	254	336	12,6
TOTAL				7,0	264,0			
MEAN				0,3	12,6			27,2
ST.DEV.				0,6	2,0			12,3

High dose group (90 mg/kg)

FEMALE		CORP. LUTEA	IMPL.	EMBRYONIC DEATHS	LIVE FETUSES	BW D6	BW D21	CORR. BW GAIN (GR)
67		14	11	2	9	242	347	40,5
68		14	14	0	14	253	378	36,6
69		14	14	0	14	251	369	23,7
70		9	9	3	6	242	321	37,2
71	<NP>					256	253	0,0

72	<NP>					242	253	0,0
73		11	11	2	9	257	353	30,3
74		13	13	0	13	255	360	19,9
75		16	14	11	3	262	311	26,0
76		15	15	9	6	264	322	18,1
77		13	13	0	13	281	378	11,2
78		16	14	2	12	252	351	19,0
79		15	13	0	13	270	352	-5,5
80		13	13	4	9	277	352	9,3
81		14	12	0	12	259	309	-25,6
82		16	16	13	3	256	299	20,2
83		16	12	1	11	263	359	24,0
84		14	14	0	14	278	333	-30,5
85		16	16	7	9	278	362	19,5
86		14	14	9	5	259	315	22,2
87		14	13	5	8	265	352	31,5
88		15	14	12	2	287	318	10,2
TOTAL				80,0	185,0			
MEAN				4,0	9,3			16,9
ST.DEV.				4,5	4,0			18,8

To our knowledge, there is no data available on any of the four constituents and it was indicated by the registrant that they are not produced as separate entities.

The two cleft lip malformations were observed in separate litters. Extended summaries from six studies were available as historical control data, which included detailed results from the visceral examinations. No cleft/misshapen/absent palate's were observed in any of these studies.

Page 8 in Annex I: this is indeed a mistake, the last (half)sentence should have been deleted.

RAC's response

RAC notes the support for the proposed classification in Repr. 1B – H360D.
The individual data on body weights and intra uterine data, which was requested by the commenting member state, has been very helpful for RAC. As the DS has concluded, it is clear from the data there is no correlation between post-implantation loss and effects on the corrected maternal body weight gain.

Date	Country	Organisation	Type of Organisation	Comment number
16.01.2017	Belgium		MemberState	6

Comment received

No data are available on the effect of the substance on sexual functions or fertility. Two 90-d repeated dose toxicity studies on rats and dogs did not show any effect on reproductive organs.
One OECD prenatal test study was performed on female WISTAR rats. Dams showed a reduction of body weight, body weight gain and food consumption at 90 mg/kg bw/d and no effects were found in females exposed to 30 or 10 mg/kg bw/d. NOAEL (mat) 30 mg/kg bw/d, LOAEL (mat) 90 mg/kg bw/d.
At 90 mg/kg bw/d, a 30% post-implantation loss rate was observed. External abnormalities (head) were seen in 2.7 % of the fetuses, 4% presented a decrease in body

weight, 60% an altered texture of cut surface of the eye lens, 8% abnormalities of the cervical vertebra and 6% abnormalities of the cranial bone. At 30 mg/kg bw/d, 23% of the fetuses presented an altered texture of the surface of eye lens and 3% an abnormality of the cervical vertebra. The NOAEL was set up at 10 mg/kg bw/d and the LOAEL at 30 mg/kg bw/d. Effects appearing at 30 mg/kg bw/d did not cause any sign of toxicity in mothers, showing that fetuses were more sensitive than their mothers to the test substance. Alteration of the texture of cut surface of the eye lens and abnormalities of the cervical vertebra were observed in a dose-dependent way and in different fetuses of different litters, which increases the concern about the test substance potential to cause fetotoxic effects. Alteration of the surface of the eye lens can happen as an analysis artefacts, but in this case, BE CA agrees that the incidence and the dose-dependency, as well as the fact that cataracts were already observed in animals of a 90-d repeated toxicity dose on rats, all show that it is a severe effect on the eye and fetuses may be more sensitive to the test substance. No data allow to determine the sensitivity and the relevance of the toxic mechanisms in humans, but considering the fetotoxic effects, their severity and the sensitivity of the organisms in development, BE CA agrees with the dossier submitter to classify as Repr. 1B, H360D.
Dossier Submitter's Response
Thank you for your comments and your support.
RAC's response
RAC notes the support for the proposed classification in Repr. 1B – H360D.

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2017	United Kingdom	<confidential>	Company-Manufacturer	7
Comment received				
We shared all company data with RIVM during preparation of the CLH dossier				
Dossier Submitter's Response				
Thank you for providing these data.				
RAC's response				
RAC is very grateful that IND had the possibility and willingness to share company data with both the DS and with RAC during this process. RAC notes that no comment was provided on the proposed classification.				