Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Tetrahydrofurfuryl methacrylate

EC Number: 219-529-5
CAS Number: 2455-24-5

CLH-O-0000007312-82-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TETRAHYDROFURFURYL METHACRYLATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: Tetrahydrofurfuryl methacrylate
EC number: 219-529-5
CAS number: 2455-24-5
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2022	United Kingdom	Mitsubishi Chemical Corporation	Company-Manufacturer	1
Comment received				
No comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH proposal_THFMA_CAS 2455-24-5_comments from LIAlphaBV_OR_MCCJapan_15_Aug_2022_revC.docx				
Dossier Submitter's Response				
For response to the provided comments please see comments number 6 and 10.				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
08.08.2022	Germany		MemberState	2
Comment received				
Both classification proposals, the one for fertility and the one for developmental toxicity, are justified by the same effect, the loss of offspring. In the justification for the classification in Repr. 1B for fertility, this effect is described as "pre-birth death", and in the justification for the classification in Repr. 1B for developmental toxicity as "total litter loss". In both arguments, the loss of offspring or the reason for the loss of offspring is not sufficiently and comprehensibly described. In the view of the DE CA, "pre-birth death" may mean late resorptions, which are to be assigned as an effect of developmental toxicity. Thus, there is insufficient justification for a classification in Repr. 1B for fertility.				
Dossier Submitter's Response				
For response please see Comment No 7.				

RAC's response
Same, see response to comment 7.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	Finland		MemberState	3

Comment received

The dossier submitter proposes to classify the substance (THFMA) Repr. 1B; H360FD based on the results of the OECD TG 422 study. We agree that resorptions, post-partum pup mortality and total litter losses provide clear evidence of adverse effect on development thus warranting classification for Repr. 1B; H360D. The evidence for adverse effect on fertility and sexual function is not as clear, since no actual effects on fertility (e.g., on oestrus cycle, gametes, implantation) are reported for the substance. The mean pre-coital interval is only slightly increased in low and high dose females seemingly due to a few individuals. It could also be considered whether resorptions and pup mortality are in the scope of fertility and sexual function or only in the scope of developmental toxicity. Nevertheless, we agree that increased gestation length of high dose dams is significant treatment related effect although this endpoint is compromised by a low number of gravid control dams.

According to the CLH report, THFMA is expected to rapidly hydrolyze to Tetrahydrofurfuryl alcohol, which is also impurity in the boundary composition of the registered substance. We note that Tetrahydrofurfuryl alcohol has harmonized classification Repr. 1B; H360Df based on effects that have similarities with the present substance. Prolonged gestation length, resorptions, and pup mortality, but also effects on testes with impaired spermatogenic activity and prolonged oestrus cycle were reported for Tetrahydrofurfuryl alcohol. Both substances cause thymus atrophy and haemological effects.
We propose to consider the database of Tetrahydrofurfuryl alcohol and RAC conclusions on Tetrahydrofurfuryl alcohol when deciding whether Repr. 1B; H360F or Repr 2; H361f is appropriate classification for THFMA.

Dossier Submitter's Response

Thank you for your support of Repr. 1B, H360D.

For the assessment of reproductive toxicity a combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test with testing up to a dose of 300 mg/kg bw/d and 10 animals per dose is available.
Adverse effects on sexual function and fertility are defined in more detail in the ECHA guidance Chapter R.7a (2017); beside others "pregnancy outcome" is one parameter to be considered. Monograph No 31 (ECETOC 2002) on the other hand limit effects to be considered for impairment of fertility till implantation into the uterine endometrium; effect on the further development should be considered for developmental toxicity. Therefore we agree that it can be discussed if resorptions and pre-birth loss are in the scope of fertility and sexual function or only in the scope of developmental toxicity.

The increase of the pre-coital interval in the mid-dose group (120 mg/kg bw/d) was related to one female which mated 14 days after pairing. The increase in the high dose group, however, has to be assessed as substance related. For further details see table below (data not presented in the CLH report).

Pre-coital interval (number of days paired to sperm positive day) (Anonymous 2015)

	control	50 mg/kg bw/d	120 mg/kg bw/d	300 mg/kg bw/d
Individual animal data n=10/dose	3	4	2	5
	1	3	3	3
	4	1	4	9
	3	1	4	6
	4	1	1	1
	4	3	1	3
	2	4	1	2
	4	2	1	5
	3	4	1	4
	1	4	14	4
Mean SD	**2.9 ± 1.20**	**2.7 ± 1.34**	**3.2 ± 3.99**	**4.2 ± 2.25**

Due to the screening character of the study gestation length can only be based on a small number of dams, however, statistical significance (CLH report, table 31 and 32), supported by results with the metabolite tetrahydrofurfuryl alcohol (THFA) (documenting prolongation of gestation length with a mean value of 24.7 days at 150 mg/kg/day THFA, compared with 22.6 days in controls) strengthens the parameter.

We agree that the available data with tetrahydrofurfuryl alcohol[1] (EC 202-625-6), which is a metabolite of THFMA, supports the classification of THFMA for reproductive toxicity. Oral exposure (OECD 421) to tetrahydrofurfuryl alcohol, like for THFMA, resulted in prolonged gestation, resorptions and pup loss. Effects on testes have been documented only for the highest dose tested (500 mg/kg bw) and therefore cannot directly be compared with the negative results for THFMA at 300 mg/kg bw in males. The mean estrous cycle was significantly prolonged also only at 500 mg/kg/d.
Tetrahydrofurfuryl alcohol has a harmonized classification as Repr 1B, H360fD and is included in the (boundary) composition in concentrations above the generic concentration limit for CMR Cat 1B of 0.3% (Table 3.7.1, CLP).

RAC's response

Some information from the RAC CLH opinion on THFA is included in the opinion. Consistent with the classification of THFA, THFMA is classified as Repro 1B; H360Df. For developmental toxicity, this is based on the pre-birth death and total litter loss. For fertility, this is based on the adverse effects on gestational length and pregnancy outcome.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2022	France		MemberState	4

Comment received

Fertility:

Table 25: absolute weight for uterus is very high at 300 mg/kg bw/day with also a high SD. Do you have any explanation for this result? This may be due to the abnormal size of uterus found in 2 females?

We note that the fertility index is rather low in the control group (4/10 females not pregnant) that can decrease the level of confidence in the OECD 422 study. Are there any relevant HCD available in order to check if the fertility index in the control group is still in a normal biological range?

[1] tetrahydrofurfuryl alcohol Registry of CLH intentions until outcome - ECHA (europa.eu)

The most critical effect on fertility reported in this study is the increase of gestation length that is clearly dose related and associated with litter loss. Based on this effect, the proposed classification as Repr. 1B for fertility is supported. Moreover, it is noted that pre-coital interval is also increased.

Development:
The proposed classification is based on total resorption and total litter loss found in the OECD 422 study. As total litter loss can be secondary to the increased gestation length, FR questions if this effect is not already covered by the classification for fertility. Anyway, the increase of total resorption can justify a classification for developmental toxicity.

Dossier Submitter's Response

Absolute uterus weights were increased in all dosed females; mean relative uterus weight was increased about 3-fold in the 300 mg/kg bw/d group. However, it has to be noted that females have been sacrificed on different points in time: females with live pups were killed on day 4 post partum; females with total litter loss were killed on the day of occurance of total litter loss. One female with total litter loss sacrified on day 0 post partum gave the most diverging result. For further details see tables below.

Absolute uterus weights [g], individual animal data including macroscopic observation and gestation length for high dose dams (Anonymous 2015)

	control	50 mg/kg bw/d	120 mg/kg bw/d	300 mg/kg bw/d		
Individual animal data n=10/dose	0.505	0.798	1.031	0.739	Sacrified on day 4 post partum, total litter loss	Gestation 25 days
	0.477§	0.757	1.078	1.351	Sacrified on day 4 post partum, total litter loss	Gestation 24 days
	0.831	0.878	0.627	7.417	Sacrified on day 0 post partum, total litter loss	Gestation 25 days
	0.544§	0.796	1.185	1.148	Sacrified on day 4 post partum, total litter loss	Gestation 22 days
	0.713	0.809	0.852	1.959	Sacrified on day 26 of gestation, total resorption	-
	0.881	0.825	0.631§	1.042	Sacrified on day 4 post partum, total litter loss	Gestation 24 days
	0.521§	0.641#	0.907	1.646	Sacrified on day 28 of gestation, abnormal size, thickened right horn, total resorption	-
	0.664	1.046	0.579	1.098	Sacrified on day 4 post partum, total litter loss	Gestation 25 days
	0.735	0.808	0.520	0.978	Sacrified on day 4 post partum, total litter loss	Gestation 25 days
	0.563§	0.845	1.233	2.766	Sacrified on day 26 of gestation, abnormal size (distended), total resorption	-
Mean SD	**0.643 ± 0.143**	**0.820 ± 0.101**	**0.864 ± 0.264**	**2.014 ± 1.988**		

§ not pregnant, # unilateral implantation

Relative uterus weights [g] (organ to body weight ratio), individual animal data (Anonymous 2015)

	control	50 mg/kg bw/d	120 mg/kg bw/d	300 mg/kg bw/d
Individual animal data n=10/dose	0.138	0.259	0.326	0.232
	0.156	0.242	0.365	0.450
	0.274	0.274	0.198	2.036
	0.183	0.254	0.361	0.417
	0.253	0.255	0.287	0.629
	0.280	0.230	0.188	0.335
	0.199	0.195	0.303	0.530
	0.227	0.365	0.187	0.376

	0.239	0.262	0.169	0.352
	0.220	0.240	0.341	0.907
Mean SD	**0.217 ± 0.048**	**0.258± 0.044**	**0.272 ± 0.079**	**0.627 ± 0.530**

Historic control data from the testing laboratory are not presented in the study report.

Thank you for the support of Repr. 1B for fertility and a classification for development at least based on total resportions seen in high dose females.

RAC's response

Additional information is noted.
Consistent with the classification of THFA, THFMA is classified as Repro 1B; H360Df. For developmental toxicity, this is based on the pre-birth death and total litter loss. For fertility, this is based on the adverse effects on gestational length and pregnancy outcome.

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2022	France		MemberState	5

Comment received

Fertility:
Table 25: absolute weight for uterus is very high at 300 mg/kg bw/day with also a high SD. Do you have any explanation for this result? This may be due to the abnormal size of uterus found in 2 females?
We note that the fertility index is rather low in the control group (4/10 females not pregnant) that can decrease the level of confidence in the OECD 422 study. Are there any relevant HCD available in order to check if the fertility index in the control group is still in a normal biological range?
The most critical effect on fertility reported in this study is the increase of gestation length that is clearly dose related and associated with litter loss. Based on this effect, the proposed classification as Repr. 1B for fertility is supported. Moreover, it is noted that pre-coital interval is also increased.

Development:
The proposed classification is based on total resorption and total litter loss found in the OECD 422 study. As total litter loss can be secondary to the increased gestation length, FR questions if this effect is not already covered by the classification for fertility.
Anyway, the increase of total resorption can justify a classification for developmental toxicity.

Dossier Submitter's Response

See response to comment No 4

RAC's response

Same, see respons to comment 4.

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2022	United Kingdom	Mitsubishi Chemical Corporation	Company-Manufacturer	6

Comment received

1) CLH proposal to assign Repr 1B; H360 FD
We disagree with the proposal to include the F classification in H360 FD, as we conclude that the longer times for mating, gestation length, and pre-coital are not significant

enough to warrant the F classification. We agree that the data reported in the OECD 422 Combined Repeated Dose toxicity study with the Reproductive/developmental toxicity screening test in rats did observe slight increases in time for mating, gestation length, and pre-coital intervals.

However on closer inspection, some of the data can be seen to have extreme outliers (an example can be found in the OECD 422 report for study no. 96310 Group 3 regarding pre-coital interval). Extreme outliers would then increase the median values and standard deviations for the pre-coital interval. In group 3 the standard deviation (3.99) in the mid dose study is higher than the mean value (3.2), and in high dose group there is also a quite high standard deviation (standard deviation 2.25 versus a mean of 4.2) and therefore these are not statistically significant data for pre-coital intervals.

We believe that these outliers are either errors in the assessment or are extremely unrepresentative data results. It should be noticed that the majority of the data falls within expected pre-coital interval for rats.

We recommend that the hazard classification of THFMA should remain as Repr 1B; with hazard statement code H360D.

We also recognise that the F classification can be determined from the high THF alcohol boundary composition (lead dossier <=1%). However we believe that the actual composition of the residual THF alcohol is much lower than this dossier boundary composition. Therefore we propose to confirm the low residual THF alcohol this by carrying out a co-registrant survey and update the dossier accordingly.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH proposal_THFMA_CAS 2455-24-5_comments from LIAlphaBV_OR_MCCJapan_15_Aug_2022_revC.docx

Dossier Submitter's Response

Concerning pre-coital intervals: The outliers in the 120 mg/kg bw/d group is documented in the CLH report (page 31) and no considered relevant for classification (a NOAEL of 120 mg/kg bw has been derived). High dose females show a clear trend for an increased pre-coital interval, although the number of animals is limited. For individual animal data see response to comment No 3.
Unfortunately, historic control data are not presented in the study report and therefore could not be used for the dossier.

Thank you for the information on the maybe lower amount of THFA (EC 202-625-6) in the boundary composition. The CLH Dossier has been prepared based on the information in the latest available registration data. It also has to be mentioned that THFA is a metabolite of THFMA, showing similar effects and supporting the classification of THFMA.

RAC's response

Information is noted.
Consistent with the classification of THFA, THFMA is classified as Repro 1B; H360Df. For developmental toxicity, this is based on the pre-birth death and total litter loss. For fertility, this is based on the adverse effects on gestational length and pregnancy outcome.

Date	Country	Organisation	Type of Organisation	Comment number
08.08.2022	Germany		MemberState	7

Comment received

The proposed classification of THFMA as Repr. 1B, H360 for fertility and developmental toxicity is based on a combined repeated oral dose toxicity study in rats with a screening test for reproductive and developmental toxicity according to OECD TG 422 (Anonymous 2015). In this study, ten male and ten female rats were treated with 0, 50, 120 and 300 mg/kg bw/d, respectively.

Fertility:
The DE CA does not support the proposal to classify THFMA in Repr. 1B for fertility.

The classification proposal of THFMA in Repr. 1B for fertility to be based on the prolonged gestation period and the loss of offspring described as "pre-birth death" is questionable.

Prolongation of the gestation period alone may not be considered to be an adverse effect. An association between the prolonged gestation period of animals in the highest dose group and the loss of offspring cannot be sufficiently substantiated in this report.

The second argument for the classification of the substance for fertility given is the loss of offspring, which the authors of the study Anonymous 2015 refer to as "pre-birth death". The classification proposal does not sufficiently document and describe what exactly is meant by this term and what this effect may be based on. According to the authors of the study, dystocia, i.e. a severe course of birth, is not mentioned as a reason for the loss of the offspring. Stillbirths are also not listed in the report. This leads to the conclusion that the loss of offspring may be due to late resorptions - which as an adverse effect should be attributed to developmental toxicity and not fertility.

Neither the prolonged gestation period nor the late resorptions, which may be termed "pre-birth death", are a justification for classification in Repr. 1B, fertility. For this reason, this classification proposal is not supported.

Developmental toxicity
The proposed classification of THFMA in Repr. 1B, H360 for developmental toxicity is supported.

The classification proposal is justified by the effects observed in the combined repeated oral dose toxicity study in rats with a screening test for reproductive and developmental toxicity according to OECD TG 422 (Anonymous 2015). In the highest dose group (300 mg/kg bw/t), total resorptions were observed in three out of ten females and total litter loss in seven out of ten females. The reason given for the total litter loss was "pre-birth death". As explained above, the effect of "pre-birth death" is understood as late resorption, and thus justifies a classification in Repr. 1B, developmental toxicity. Therefore, the proposed classification Repr. 1B, H360 for developmental toxicity is agreed.

Dossier Submitter's Response

The correct definition of the term "pre-birth loss" is missing in the CLH report. In the study report pre-birth loss has been calculated as a percentage from the following formular:

(No. of visible implantations – total litter size at birth) x 100 / (No. of visible implantations)

Pre-birth loss therefore do not consider dead born pups (see table below columns 6-8). Total litter loss on the other hand includes also pups who died after parturition.
It has to be noted that in general in this study only visible implantations were counted; only uteri of females with no visible implantations have been immersed in a 10-20% solution of ammonium sulphide to reveal evidence of non visible implantation.

For a better overview on the correlation of gestation length of dams, pup survival and pup viability in the high dose group (300mg/kg bw/d) see the following table:

Animal identifcation	Macroscopic/ microscopic observation in uterus	Corpora lutea	Implan-tations	Pre-implantation loss [%]	Total litter size at birth	Pre-birth loss [%]	Live litter size at birth	Gestation length [days]	Clinical sign of live pups (day)
96360061	total litter loss	13	13	0.0	1	92.3	1	25	Could to touch, no food intake. (0), missing (1)
96360063	total litter loss	16	16	0.0	4	75.0	2	24	Could to touch, no food intake (0), missing (1)
96360065	total litter loss	16	16	0.0	8	50.0	0	25	-
96360067	total litter loss	18	18	0.0	15	16.7	11	22	No food intake (0), found dead or missing (1)
96360069	total resorption (visible implantations only after ammonium sulphide solution immersion)	16	16	0.0	-	-	-	-	-
96360071	total litter loss	16	16	0.0	8	50.0	2	24	Could to touch, no food intake (0), missing (1)
96360073	abnormal size, thickened right horn, total resorption (4 left, 10 right)	15	14	6.7	-	-	-	-	
96360075	total litter loss	17	17	0.0	2	88.2	2	25	Could to touch, no food intake (0), missing (1)
96360077	total litter loss	12	9	25.0	1	88.9	1	25	Could to touch, no food intake (0), missing (1)
96360079	abnormal size (distended),	14	14	0.0	-	-		-	

	total resorption (7 left, 7 right)								

Dystocia is not reported. Dead born pups are documented for 4 dams (column 6 vs 8). Live pups (in bad condition) were missing or died on day 1.

A classification for fertility is proposed based on a prolongation of gestation length, the increased pre-birth loss (including early and late resorptions) as well as a slight increased pre-coital interval.

Thank you for supporting Repr. 1B for development.

RAC's response

Information is noted.
Consistent with the classification of THFA, THFMA is classified as Repro 1B; H360Df. For developmental toxicity, this is based on the pre-birth death and total litter loss. For fertility, this is based on the adverse effects on gestational length and pregnancy outcome.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2022	France		MemberState	8

Comment received

Skin Sensitisation: FR supports the proposed classification as Skin Sens. 1A.

THFMA is negative in experimental animals in a non-reliable study. Various human data are available. The frequencies of skin reactions are generally above 2% (except in two studies: Vilaplana et al. 2000 and IVDK, 2001). The frequencies set by Gatica-Ortega et al. 2017 and by Aalto-Korte et al., 2008 are certainly over-estimated and should be taken with caution when comparing to criteria set in the CLP Regulation. Indeed, the patients who were patch tested with THFMA are already sensitized to (meth)acrylates. Finally, THFMA is positive in all in vitro studies performed.

Overall, THFMA is a clear skin sensitizer agent. Based on tables 3.2 and 3.3 of CLP guidance, there are a high frequency of occurrence of skin reactions and a relatively low exposure (score = 4). Thus, this corresponds to subcategory 1A based on table 3.4 of CLP guidance.

Upper respiratory tract symptoms and rhinitis are reported in human data (Gativa-Ortega et al. 2017 and Kanerva et al. 1995). Do you consider the need for classification as an irritant and/or sensitiser agent to respiratory tract? Indeed, THFMA is a volatile substance (27 Pa) and some volatile methacrylates also present these hazard properties (e.g see RAC opinion on MMA and conclusion documents on HEMA/HPMA [classification proposals for this properties are planned by France]).

Dossier Submitter's Response

Thank you for supporting Skin Sens. 1A.

Respiratory tract irritation/sensitisation has not been evaluated due to lack of data. No data on occupational asthma have been identified with the substance.
Gatica-Ortega (2017) investigated files of 2353 patch tested patients in four dermatology departments in Spain. A diagnosis of ACD caused by (meth)acrylates in long-lasting nail polish was made in 43 females (1.82% of all patients; 2.84% of the 1514 females patch

tested). The allergens that were most frequently positive in the tests were: 2-hydroxypropyl methacrylate (HPMA), 2-hydroxyethyl methacrylate (HEMA), and tetrahydrofurfuryl methacrylate (THFMA). All patients except for 1 reacted to HPMA. In all cases, multiple positive reactions were recorded. THFMA was positive in 31/39 patients tested. The study also reports that 6 patients (14%) had upper respiratory tract symptoms such as throat discomfort, hoarseness or congestion, however, a direct link to THFMA exposure cannot be made based on the presented data.
Kanerva (1995) reports the case of a 38-year old woman working with a glue containing acrylates/methacrylates. Here symptoms among others included rhinitis. Also here a direct link to THFMA exposure cound not be established due to exposure to several acrylates/methacrylates.

RAC's response
Information is noted.

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2022	France		MemberState	9

Comment received
Skin Sensitisation: FR supports the proposed classification as Skin Sens. 1A. THFMA is negative in experimental animals in a non-reliable study. Various human data are available. The frequencies of skin reactions are generally above 2% (except in two studies: Vilaplana et al. 2000 and IVDK, 2001). The frequencies set by Gatica-Ortega et al. 2017 and by Aalto-Korte et al., 2008 are certainly over-estimated and should be taken with caution when comparing to criteria set in the CLP Regulation. Indeed, the patients who were patch tested with THFMA are already sensitized to (meth)acrylates. Finally, THFMA is positive in all in vitro studies performed. Overall, THFMA is a clear skin sensitizer agent. Based on tables 3.2 and 3.3 of CLP guidance, there are a high frequency of occurrence of skin reactions and a relatively low exposure (score = 4). Thus, this corresponds to subcategory 1A based on table 3.4 of CLP guidance. Upper respiratory tract symptoms and rhinitis are reported in human data (Gativa-Ortega et al. 2017 and Kanerva et al. 1995). Do you consider the need for classification as an irritant and/or sensitiser agent to respiratory tract? Indeed, THFMA is a volatile substance (27 Pa) and some volatile methacrylates also present these hazard properties (e.g see RAC opinion on MMA and conclusion documents on HEMA/HPMA [classification proposals for this properties are planned by France]).
Dossier Submitter's Response
See response to comment No 8.
RAC's response
Same, see response to comment 8.

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2022	United Kingdom	Mitsubishi Chemical Corporation	Company-Manufacturer	10
Comment received				
2) CLH proposal to assign Skin Sens. 1A; H317 We do not agree that THFMA is required to be sub-classified as Skin Sens 1A; and believe the data is only sufficient to warrant a classification of Skin Sens 1. We are aware that the human patch test data for methacrylates (including THFMA) can result in misleading results because of the cross reactivity and allergy sensitisation from other sources of methacrylates. Within the CLH proposal document from the Austrian competent authority, this cross allergy effect was also highlighted and mentioned. Therefore the evidence in the CLH proposal discussing the observed sensitisation effects of THFMA from the various human patch studies must be taken with caution. Since these patch test studies involve many methacrylate and other chemicals (including glutaraldehyde, acrylates and formaldehyde). Such studies are not specific to THFMA and the evidence is not conclusive sufficiently to determine that THFMA causes widespread sensitisation in human studies. The in-vitro skin sensitisation data (LuSens, DPRA, MUSST) can only confirm THFMA is a skin sensitiser and not its potency. We believe that Skin Sensitisation Category 1 is justified as the human patch test data is not reliable enough to assign THFMA as a subcategory 1A. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH proposal_THFMA_CAS 2455-24-5_comments from LIAlphaBV_OR_MCCJapan_15_Aug_2022_revC.docx				
Dossier Submitter's Response				
Cross reactivity among methacrylates is known and reported in the dossier. No standard animal test with THFMA but positive in vitro skin sensitisation data are available. Human data demonstrate a high frequency of occurence of (cross)sensitization; in combination with low doses needed for elicitation classification as Skin Sens. 1A is indicated. The Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a (ECHA, 2017) states: "*Evidence of skin sensitising activity derived from diagnostic testing may reflect the induction of skin sensitisation to the substance tested or cross-reaction with a chemically very similar substance. In both situations, the normal conclusion would be that this provides positive evidence of the skin sensitising activity of the substance used in the diagnostic test.*"				
RAC's response				
The potential of cross-sensitisation to other methacrylates is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.08.2022	Germany		MemberState	11
Comment received				
The proposal for classification of THFMA as Skin Sens. 1 with subgrouping into category 1A, H317, is considered justified and supported.				

Based on the documented high occurrence of reactions in occupationally exposed population and on positive results for three key events in the AOP for skin sensitisation detected in the available in chemico/in vitro tests (DPRA, LuSens, MUSST), a weight-of-evidence approach justifies the classification as Skin Sens. 1A, H317. More recent IVDK data on the occurrence of sensitisation to THFMA (not cited in the CLH report) can be found in the BAuA report "Frequency of skin sensitization to specific substances and in specific occupational groups", 2021. Table 3.2.1.2 of the BAuA report lists positive reactions to various allergens in patients with occupational (OD-patients) and with non-occupational (non OD-patients) dermatitis. According to BAuA publication, 41/950 occupationally exposed dermatologic patients are sensitised to THFMA 4.3 % (95 % - CI: 3.1 % - 5.8 %) and 29/6696 non-occupationally exposed dermatologic patients are sensitised to THFMA 0.4 % (95 % - CI: 0.3 % - 0.6 %). It should be noted that the test persons in the studies were exposed to different methacrylates and probably also showed positive reactions with these methacrylates. The possibility of cross-reaction cannot be ruled out, but it does not interfere with the proposed classification. THFMA also contains the substance methyl methacrylate (MMA) as an impurity which also has sensitising properties for the skin and respiratory tract. MMA is classified as Skin Sens. 1, H317 harmless and is present in the composition at concentrations up to the general concentration limit (GCL) of ≥ 1 %.
Dossier Submitter's Response
Thank you for supporting Skin Sens. 1A. Thank you for presenting additional supporting information from IVDK, based on data from 2007 to 2016. (link to the English report: BAuA - baua: Bericht - Frequency of skin sensitization to specific substances and in specific occupational groups - Bundesanstalt für Arbeitsschutz und Arbeitsmedizin)
RAC's response
The BAUA report (2021) is based on the IVDK database, from 2007-2016. This database contains data from 120,977 patch tested patients. In 15.6% of these patients, Occupational Dermatitis (OD) was diagnosed, while in 72.7% non-occupational dermatitis was determined (with 11.7% not document whether the dermatis was occupational or not). The percentage of positive reactions to TFHMA reported is 75 out of 8434 (unselected dermatitis) patients (0.9% with 95%-CI of 0.7-1.1%). In patients with OD, 41 patients reacted positive out of 950 tested (4.3 % with 95%-CI: 3.1-5.8%). In patients without OD, 29 patients reacted positive out of 6696 (0.4% with 95%-CI: 0.3-0.6%). Information is added to the RAC opinion.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2022	France		MemberState	12
Comment received				
STOT RE: FR agrees that no classification is warranted based on the OECD 422 study.				
Dossier Submitter's Response				
Thank you for your agreement.				

RAC's response
Response noted.

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2022	France		MemberState	13
Comment received				
STOT RE: FR agrees that no classification is warranted based on the OECD 422 study.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
Response noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2022	United Kingdom	Mitsubishi Chemical Corporation	Company-Manufacturer	14
Comment received				
No comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH proposal_THFMA_CAS 2455-24-5_comments from LIAlphaBV_OR_MCCJapan_15_Aug_2022_revC.docx				
Dossier Submitter's Response				
See response to comment No 6 and 10.				
RAC's response				
See earlier responses.				

PUBLIC ATTACHMENTS
1. CLH proposal_THFMA_CAS 2455-24-5_comments from LIAlphaBV_OR_MCCJapan_15_Aug_2022_revC.docx [Please refer to comment No. 1, 6, 10, 14]