Committee for Risk Assessment

RAC

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

8 June 2023

CLH-O-0000007312-82-01/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: **Tetrahydrofurfuryl methacrylate**

EC Number: **219-529-5**

CAS Number: **2455-24-5**

The proposal was submitted by **Austria** and received by RAC on **19 May 2022.**

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

PROCESS FOR ADOPTION OF THE OPINION

Austria 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 **14 June 2022**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **15 August 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Gerlienke Schuur**

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 **8 June 2023** by **consensus**.

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

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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	No current Annex VI entry										
Dossier submitters proposal	TBD	Tetrahydrofurfuryl methacrylate	219-529-5	2455-24-5	Skin Sens. 1A Repr. 1B	H317 H360FD	GHS07 GHS08 Dgr	H317 H360FD			
RAC opinion	TBD	Tetrahydrofurfuryl methacrylate	219-529-5	2455-24-5	Skin Sens. 1A Repr. 1B	H317 H360Df	GHS07 GHS08 Dgr	H317 H360Df			
Resulting Annex VI entry if agreed by COM	TBD	Tetrahydrofurfuryl methacrylate	219-529-5	2455-24-5	Skin Sens. 1A Repr. 1B	H317 H360Df	GHS07 GHS08 Dgr	H317 H360Df			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Tetrahydrofurfuryl methacrylate (THFMA) is used as a monomer in polymerisation and in coating, adhesive and sealant formulations. It is only used at industrial sites and by professional workers. The use of THFMA by professionals in mixtures containing the liquid monomer when coming into contact with skin or nails is advised against (Registration dossier).

The substance may contain impurities which contribute to the classification and labelling, namely methyl methacrylate (CAS Number 80-62-6) with a classification as Flam Liq. 2, H225; Skin Irrit. 2, H315; Skin Sens. 1, H317 and STOT SE3, H335, and tetrahydrofurfuryl alcohol (THFA; CAS Number 97-99-4) with a classification as Eye Irrit. 2, H319 and Repr. 1B, H360Df.

Toxicokinetics

No toxicokinetic studies for THFMA are available. Based on analogy to alkyl-methacrylate esters, it is noted that they are initially hydrolysed by non-specific carboxylesterases to methacrylic acid and the corresponding alcohol in several tissues and in blood. Recent investigations with related substances show a short half-life within the body and effective removal (first pass through liver) of systemically absorbed parent ester. Because of the structural similarity of THFMA to other alkyl-methacrylate esters, rapid hydrolysis to tetrahydrofurfuryl alcohol is expected in the order of minutes.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

In chemico and *in vitro* assays (a Direct Peptide Reactivity Assay - DPRA, a keratinocyte based ARE Reported Gene Assay - LuSens, and a Myeloid U937 Skin Sensitization Test - MUSST, recently also called U-SENS) resulted in a positive outcome for three key events in the Adverse Outcome Pathway (AOP) for skin sensitisation.

One guinea pig study was available, which was assessed to be not reliable.

Several retrospective studies based on filed patch-tests are available, which focussed on beauticians, dental staff/patients and workers with exposure to (meth)acrylates. Positive reactions in patients in the different studies ranged from 2.7-80.0%.

The Dossier Submitter (DS) noted that it can be assumed that there was exposure to different methacrylates, and most of them also had positive patch-test results for more than one methacrylate.

DS proposed Skin Sens. 1A, H317, based on the human evidence showing a high frequency of occurrence of skin sensitisation combined with the low exposure needed for elicitation. This conclusion is supported by the positive results for three key events in the AOP for skin sensitisation from the *in chemico* and *in vitro* assays.

The DS could not propose a Specific Concentration Limit (SCL) as no robust data on potency of THFMA is available.

The DS remarked that the registered substance THFMA contains an impurity (methyl methacrylate) classified as Skin Sens. 1, H317, which is included up to the generic concentration limit (GCL) of of ≥ 1%. However, as the substance THFMA itself shows clear sensitising properties *in vitro* and in humans the impurity has not been considered further.

Comments received during consultation

Two Member States Competent Authorities (MSCAs) supported the proposed classification as Skin Sens. 1A based on the human data and supported by the positive results for three key events in the AOP for skin sensitisation in *in vitro* tests. One MSCA noted that frequencies set by two studies (Gatica-Ortega et al. 2017; Aalto-Korte et al., 2008) were over-estimated and should be taken with caution, as the study subjects were already sensitised to (meth)acrylates. Sub-category 1A is supported based on the high frequency of occurrence of skin reactions and a relatively low exposure (score=4). The other MSCA brought forward more recent data from the Information Network of Departments of Dermatology for recording and scientific analysis of contact allergies (IVDK, BAUA report, 2021). It was further noted that methyl methacrylate, classified as Skin Sens. 1, is present as an impurity up to the GCL of ≥ 1%.

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 documented whether the dermatitis was occupational or not).

Positive reactions to THFMA were reported in 75 out of 8434 unselected dermatitis patients (0.9% with 95%-CI of 0.7-1.1%). In patients with OD, 41 out of 950 tested patients reacted positive (4.3 % with 95%-CI: 3.1-5.8%). In patients without OD, 29 out of 6696 tested patients reacted positive (0.4% with 95%-CI: 0.3-0.6%).

One company suggested to classify as category 1, because the data are not sufficient for subcategory 1A. Human patch test data for methacrylates (including THFMA) can be misleading because of cross-reactivity and allergy sensitisation to other sources of methacrylates. The studies are not specific enough for THFMA.

Assessment and comparison with the classification criteria

In chemico/in vitro

In the Adverse Outcome Pathway (AOP) described for Skin Sensitisation (OECD, 2014), four key events are described. For THFMA, Bauch *et al.* (2012) described three events.

Key event 1, covalent protein binding, was tested in the Direct Peptide Reactivity Assay DPRA (similar to OECD TG 442C). With THFMA, the mean peptide depletion with cysteine- and lysine-peptide was 30.0%, which indicates a positive prediction and a moderate reactivity.

Key event 2, the keratinocyte activating potential, was tested in the LuSens (similar to OECD TG 442D) assay. The antioxidant response element is tested (in two independent experiments) in modified keratinocytes with a luciferase reporter gene. THFMA showed an induction above 1.5 fold while the cellular viability was above 70%. It can be concluded that THFMA has a keratinocyte activating potential.

Key event 3, activation of dendritic cells, was tested (in two independent experiments) inMUSST(similar to OECD TG 442E). In the test, the expression of the cell surface marker CD86 is measured. THFMA did induced CD86 expression (up to 1.87 fold) with at least 70% cell viability. It can be concluded that THFMA induces dendritic cell activation.

On their own, these test results are not enough to conclude on skin sensitisation, however, taken together they suggest that THFMA is a skin sensitiser.

Animal data

Only one study with THFMA is available (Parker *et al.,* 1983, as cited in CIR, 2005). Several methacrylates in Freund's complete adjuvant were injected in the footpads of female guinea pigs four times. Seven days later, and weekly thereafter for up to 12 weeks, the substance was applied to the shaved flank of the animal. None of the tested methacrylates induced contact sensitisation. The study was assessed as not reliable by CIR (2005) and the DS, as all tested substances, even known sensitisers, tested negative.

Human data

Several studies performing retrospective analysis of patch tests are available (see Table 9 in the the CLH report):

- In patients with a history of (meth)acrylate exposure 5/147 (3.4%) showed positive reactions to THFMA (Tucker *et al.,* 1999).
- 7/258 (2.7%) patients filed at the Finnish Institute of Occupational Hygiene (FIOH) and working in dentistry were positive for THFMA (Aalto-Korte *et al.,* 2007).
- Of 10 patients filed at FIOH with occupational allergic contact dermatitis from methacrylates in glues, 7 were tested positive for THFMA (70%; Aalto-Korte *et al.,* 2008).
- Of 39 patients (beauticians) with allergic contact dermatitis caused by (meth)acrylates, 31 were tested positive for THFMA (79%; Gatica-Ortega *et al.,* 2017).

Investigation of dental staff, students or patients via patch-testing was reported by Lyapina *et al.* (2014, 2016). Positive outcomes ranged from 5.3-48.3% in the different groups for THFMA (0.2% in petrolatum).
Further information was cited in DFG (2001). Patch-tests with dental technicians (Peiler *et al.,* 2000) or patients with dental protheses (Vilaplana & Romaguera, 2000) gave positive results in 3/126 and 3/520, respectively (2.4 and 0.6%). Data from IVDK showed 5 positive cases in 298 patients (1.7%, IVDK, 2001).

More recently, the IVDK database (2001-2015) was again analysed by Heratizadeh *et al.* (2018), looking at patients diagnosed with Occupational Contact Dermatitis (OCD). In this study group, 23 out of 174 tested positive for THFMA (9.2%). BAUA (2021) also did a similar analysis on the IVDK database (2007-2016), in patients with Occupational Dermatitis (OD), 41 patients reacted positive out of 950 tested (4.3%). The percentage of positive reactions to THFMA reported is 75 out of 8434 unselected dermatitis patients (0.9%). In patients without OD, 29 out of 6696 patients reacted positive (0.4%).

According to the classification criteria of Regulation (EC) 1272/2008 (Annex I section 3.4.2.2.2) human evidence for Sub-categories 1A and 1B, respectively, can include the following type of data:

	Human data
Sub-category 1A	(a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT – induction threshold); (b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure; (c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

Sub-category 1B	(a) positive responses at > 500 µg/cm^2 (HRIPT, HMT – induction threshold); (b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure; (c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

HRIPT: Human Repeat Insult Patch Test; HMT: Human Maximisation Test

No HRIPT or HMT with THFMA are available to be able to determine an induction threshold. In the study from Lyapina *et al.* (2014/2016), a concentration of 0.2% was used, the DS calculated a dose of 70 µg THFMA/cm^2, at which elicitation is reported.

The Guidance on the Application of the CLP Criteria (Section 3.4.2.2.3.1., Table 3.2) further outlines how high or low frequency of occurrence of skin sensitisation shall be assessed), see the table below.

Table: *Relatively high or low frequency of occurrence of skin sensitisation (CLP guidance Table 3.2)*

Human diagnostic patch test data	**High frequency**	**Low/ moderate frequency**	**Information with regards to THFMA**
General population studies	≥ 0.2%	< 0.2%	Not available
Dermatitis patients (unselected, consecutive)	≥ 1.0%	< 1.0%	▪ 0.4% (26/6696 non-occupationally exposed dermatologic patients), and ▪ 0.9% (75/8434 unselected dermatitis patients) (based on IVDK data in BAUA report, 2021)
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0%	< 2.0%	▪ 3.4% (5/147; history of exposure to methacrylates; Tucker *et al.,* 1999) ▪ 48.3% (14/29; unexposed dental patients; Lyapina *et al.,* 2014) ▪ 26.5% (13/49; dental patients; Lyapina *et al.,* 2016) ▪ 0.6% (dental patients; Vilaplana & Romuguera, 2000)
Workplace studies: 1: all or randomly selected workers 2: selected workers with known exposure or dermatitis	≥ 0.4% ≥ 1.0%	< 0.4% < 1.0%	▪ 2.4% (dental technicians; Peiler *et al.,* 2000) ▪ 2.7% (7/258; dentist personnel; Aalto-Korte *et al.,* 2007) ▪ 70% (7/10; occupational exposure to glues; Aalto-Korte *et al.,* 2008) ▪ 13.8-29.6% (13/44, 9/28, 5/36 and 30/110, 2/38 and 9/65; dental students and professionals; Lyapina *et al.,* 2014/2016) ▪ 79.5% (31/39; beauticians; Gatica-Ortega *et al.,* 2017) ▪ 9.2% (OCD patients; Heratizadeh *et al.,* 2018) ▪ 4.3% (OD patients; BAUA, 2021)
Number of published cases	≥ 100 cases	< 100 cases	5+14[1)]+31+3+3+95[2)]+75[3)] = 226

1) From FIOH (7 and 7 patients from Aalto-Korte *et al.,* 2007/2008)
2) All positive patients from Lyapina *et al.,* (2014/2016)
3) IVDK (75 patients from BAUA, 2021; not double counting)

With regards to the assessment of the exposure to THFMA, see the table below.

Table: *Relative high or low exposure*

Exposure data	Indicator of relatively low exposure	Indicator of relatively high exposure	Assessment for THFMA
Concentration / dose at induction	< 1.0% < 500 µg/cm^2	≥ 1.0% ≥ 500 µg/cm^2	Concentrations in dental resins (up to 30%), nail enhancement products (up to 7%) and adhesives is relatively high. In the different patch tests, concentrations of 0.2, 2 and 5% or 70 µg/cm^2 are used (for elicitation reactions).
Repeated exposure	< once/daily	≥ once/daily	Consumers might be exposed when having applied a resin-based dental material or nail product. For professionals, the exposure might be daily.
Number of exposures (irrespective of the concentration of the sensitizer)	< 100 exposures	≥ 100 exposures	Given the type of consumer products, the use will not be daily. With regards to the professional use (nail technician and dental personnel), the exposure is highly likely more than 100 times.

Thus, in a weight-of-evidence approach, the exposure is considered low, especially for consumers.

A further point to consider is cross-reactivity, which is known to exist for methacrylates. One difficulty is that in several products (adhesives, dental resins) a combination of different methacrylates is used. With regards to classification, the DS quoted from the guidance (R7; ECHA, 2017): "*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*."

Classification

Based on the available evicence and taking into account the human data provided showing a range of incidences but overall, a high frequency of occurrence, as well as a low exposure, especially for consumers, RAC concludes that a **classification of THFMA as Skin Sens. 1A, H317 is warranted**. This is supported by the positive results found for three key events in the AOP for skin sensitisation.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Only one OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity screening) study was available, performed in male and female SD rats (N=10) dosed daily with 0, 50, 120, and 300 mg/kg bw/day via oral gavage for 29 days (males) and about 43 days (females).

The DS concluded that no relevant adverse effect with a dose-response could be identified in rats dosed orally with THFMA in concentrations up to 300 mg/kg bw/day. No classification for STOT RE is proposed.

Comments received during consultation

One MSCA agreed with no classification based on the OECD TG 422 study.

Assessment and comparison with the classification criteria

Only one OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) study (Anonymous, 2015) with THFMA is available, performed in male and female SD rats (N=10) dosed daily with 0, 50, 120, and 300 mg/kg bw/day via oral gavage for 29 days (males) and about 43 days (females).

There was a slight statistically significant decrease in food consumption in female rats during gestation in the highest dose group, with a larger decrease at PND4 (N=6, 50.8%). Body weight in female rats was statistically significantly increased at the highest dose, only at gestation day (GD) 20 (8.94%). No differences on body weight were reported in male rats. It can be concluded that there is no general marked toxicity.

Some effects were reported on organ weights; absolute and relative thymus weight were statistically significantly decreased in males at the mid and high dose (21.3%, 19.9%, and 31.3%, 31.8% respectively), and relative thymus weight in females at the highest dose (21.2%), absolute and relative adrenals weight were decreased in females at the highest dose (16.8%, 19.9%). Further, absolute uterus weight was (statistically significantly) increased at the low, mid and high dose (127.5%, 134.4%, 313.1%), and relative uterus weight at the highest dose (231.2%).

These effects on organ weights were not supported by macroscopic or microscopic observations (see Table 27 in the CLH report).

Further, some effects on haematology were reported (N=5). In male rats, dosed with 50 mg/kg bw/day and 300 mg/kg bw/day platelets were decreased (15% and 23%, respectively). Leucocytes (mainly neutrophils, lymphocytes and basophils) were decreased by 21%, 40% and 25% in males receiving 50, 120 and 300 mg/kg bw/day, respectively. Leucopenia was also recorded in females dosed with 300 mg/kg bw/day (19%). However, the decrement comprised mainly neutrophils and eosinophils. In addition, females dosed with 120 mg/kg bw/day and 300 mg/kg bw/day showed slight increase of erythrocytes, haemoglobin and haematocrit (6% to 16%) associated with reticulopenia (55%) and a slight decrease of mean corpuscular haemoglobin concentration (4%) was seen in females dosed at 300 mg/kg bw/day. A statistically significant increase of prothrombin time was recorded in animals dosed with 300 mg/kg bw/day (7% in males, 17% in females).

Classification

For a classification as STOT RE in category 2, the guidance value for a 28-day study is ≤ 300 mg/kg bw/day. In the case of THFMA, effects on organ weights were found at the highest dose of 300 mg/kg bw/day, which in the thymus was reported in both sexes and in males with a dose-response. However, this is not supported by macroscopic and microscopic findings.

RAC considers the systemic effects in the available combined rat screening study with THFMA are not severe enough and therefore **no classification for STOT RE is warranted**. RAC notes however that the available study seems to have used too low doses, and that there is a lack of studies with longer duration.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

One OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) study with THFMA was available, performed in male and female SD rats (N=10) dosed daily with 0, 50, 120, and 300 mg/kg bw/day via oral gavage for 29 days (males) and about 43 days (females).

The DS concluded that there was clear evidence of adverse effects on female fertility. The mean pre-coital interval was slightly increased and gestation length was prolonged at the highest dose (24.29 versus 22.17 days in control). Furthermore, pre-birth loss was dose-dependently increased, with 66% in the highest dose group. DS proposed a classification with Repr. 1B for adverse effects on sexual function and fertility (H360F).

With regard to developmental toxicity, effects of THFMA were found on total resorptions and total litter loos. DS proposed a classification with Repr. 1B for developmental toxicity (H360D).

The DS noted a classification for adverse effects on or via lactation were not relevant.

Comments received during consultation

Three MSCAs commented.

One MSCA noted that the proposed classifications for fertility as well as developmental toxicity were justified by the same effects, loss of offspring (noted respectively as "pre-birth death" and "total litter loss"). The MSCA assigned this as an effect of developmental toxicity and noted insufficient justification for fertility.

The comment of the second MSCA was of a similar nature. For the fertility endpoint, that MSCA agreed that increased gestation length in the high dose dams is a treatment-related effect, although compromised by a low number of gravid control dams. Further, the MS proposed to consider the database for tetrahydrofurfuryl alcohol (THFA) and RAC conclusions when deciding on category 2 or 1B for fertility.

The third MS noted that the absolute uterus weight was very high at the highest dose, and that the fertility index in the control group was rather low, and requested if historical control data (HCD) were available. Based on the increased gestation length the category 1B for fertility is supported. With regard to the litter loss, it was noted that this could be secondary to the increased gestation length. However, the increase of total resorptions justified the classification for developmental toxicity.

With regard to the questions raised, the DS responded:

- The pre-coital interval in the mid-dose group was related to one female which mated after 14 days (average 3.2 days). However, the increase in the high-dose was treatment-related (4.2±2.25 versus 2.9±12.0 in controls). Number of dams was only 10.
- With regards to THFA, a metabolite of THFMA. Oral exposure to THFA in an OECD TG 421 study resulted (also) in prolonged gestation, resorptions, and pup loss. Effects on testes have been reported in the highest dose (500 mg/kg bw/day) as well as prolonged estrous cycle, which cannot be compared with the effects in the THFMA study (highest dose 300 mg/kg bw/day). THFA has a harmonized classification as Repr. 1B, H360Df and is included in the (boundary) composition in concentrations above the generic concentration limit for classification of mixtures for reproductive toxicity of 0.3%.

- Absolute and relative uterus weights are provided. It is noted that females have been sacrificed at different points in time, females with live pups at PND4 and females with litter loss on day of litter loss.
- No HCD was presented from this laboratory in the study report.

One company disagreed with the fertility classification. They agreed on the effects reported in the OECD 422 Combined Repeated Dose toxicity study, however the company did not consider the observed slight increases in longer times for mating, gestation length and pre-coital intervals significant enough to warrant a classification for fertility. They further noted some extreme outliers.

Assessment and comparison with the classification criteria

In Anonymous (2015), an OECD TG 422 study, performed in male and female SD rats (N=10) dosed daily with 0, 50, 120, and 300 mg/kg bw/day via oral gavage for 29 days (males) and about 43 days (females), there was a slight statistically significant decrease in food consumption in female rats during gestation in the highest dose group, with a larger decrease at PND4 (N=6, 50.8%). Body weight in female rats was statistically significantly increased at the highest dose, only at gestation day (GD) 20 (8.94%). No differences on body weight were reported in male rats. It can be concluded that there is no general marked toxicity.

Absolute uterus weight was statistically significantly increased at the low, mid and high dose (127.5%, 134.4%, 313.1%), and relative uterus weight at the highest dose (231.2%).

No effect was found on testes weight, and no alterations were observed in seminiferous tubules with regard to spermatogenic cycle.

The oestrus cycle and fertility index was not affected by THFMA, up to 300 mg/kg bw/day. A slight increase was seen in the pre-coital interval, statistically significant in the mid dose (related to one female mating at 14 days), but it might be dose-dependently. The gestation length was increased, statistically significant in the high dose group. According to the study authors, this was accompanied by an increase in pre-birth loss, with about 66% in the high dose group. The report did not discuss dystocia (difficult or obstructed labor).

Table: *Information from OECD TG 422 study with THFMA with regard to reproductive parameters (N=10)*

Parameter / mg THFMA/kg bw/day	**0**	**50**	**120**	**300**
Copulatory index (%)	100	100	100	100
Pre-coital interval	2.9	2.7	**3.2***	4.2
Not pregnant	4	0	1	0
Fertility index (%)	60	100	90	100
Number of litters	6	10	9	7
Unilateral implantation	0	1	0	0
Uterus abnormal size	0	0	0	7
Total litter loss	0	0	0	7
Total resorption	0	0	0	3
With live pups on day 4 post-partum	6	10	9	0
Corpora lutea (mean number)	15.83	16.30	16.33	15.43
Implantations (mean number)	15.50	15.70	16.11	15.00
Pre-implantation loss (litters affected)	2	4	2	2
Pre-implantation loss (%)	1.97	3.29	1.26	3.57
Total Litter size at birth (mean)	14.50	14.20	13.67	**5.57***
Pre-birth loss (litters affected)	4	7	7	7
Pre-birth loss (%) **	6.52	9.34	14.64	**65.87***
Gestation length (mean days)	22.17	22.60	22.78	**24.29***

* mean value is significantly different from control $p<0.05$
** Pre-birth loss = (No. of visible implantations – total litter size at birth) x 100 / (No. of visible implantations). Please note, when trying to recalculate the pre-birth loss as provided by the dossier submitter, marginally different values are obtained. A reason for the difference is not known, but the difference does not influence the classification outcome. Data from females with total resorption or non-pregnant and from dams without live pups were excluded from group mean calculations.

For F1 offspring, the following parameters were examined: number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, body weight on days 1 and 4 post-partum. Clinical signs in pups were not affected, and no treatment-related findings (structural abnormalities, altered growth, functional deficiencies) were reported. No difference in sex ratio was noted. Body and organ weights in pups were not affected.

Table: *Information from OECD TG 422 study with THFMA with regard to offspring parameters (N=10)*

Parameter / mg THFMA/kg bw/day	**0**	**50**	**120**	**300***
Total litter size	14.50	14.20	13.67	-
Live litter size at birth	14.50	14.10	12.89	-
Liver litter size at PND4	14.50	13.40	11.56	
Pup loss (%)	0.00	0.71	5.56	
Litter weight (g) at PND1	111.03	103.41	92.39	
Litter weight (g) at PND4	151.6	141.15	117.22	
Mean pup weight (g) at PND1	7.72	7.56	7.38	
Mean pup weight (g) at PND4	10.58	10.60	10.08	
Cumulative loss (%)**	0.00	5.36	13.48	

* In 3/10 females total resorption and in 7/10 females a total litter loss is reported in the high dose group.
** Calculated as: (total litter size at birth – live litter size at day 4) x 100/total litter size at birth

Classification

<u>Developmental toxicity – comparison with the criteria</u>

No information is available in humans, thus classification in category 1A is not possible.

THFMA exposure resulted in an increase in total resorptions at the highest dose, as well as an increase in pre-birth loss (calculated as the (number of visible implantations – total litter size at

birth) x 100/ (number of visible implantations)), and a total litter loss at the highest dose. Further, there was an increase in pup loss in the middle dose group, and a slight, but not statistically significant, maybe dose-dependent, decrease in the live litter size, increasing from birth to PND4.

According to the CLP regulation (Annex I, Section 3.7.1.4) the major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

In this case, death is the effect noted in the highest dose group, as demonstrated in total litter loss. Therefore, RAC concludes that a **classification of THFMA for developmental toxicity in category 1B (Repr. 1B, H360D) is warranted**.

Sexual function and fertility – comparison with the criteria

No information is available in humans, thus classification in category 1A is not possible.

THFMA exposure resulted in a dose-dependent increase in (absolute and relative) uterus weight, and in a statistically significant increase in gestational length at the highest dose (with a possible dose-response). It is not possible to conclude if the litter loss is the result of the prolonged gestation time, and therefore a troubled parturition, or if this is a direct effect on fetuses. The effects on the fetuses (litter loss, pup loss) are taken into account in the classification for developmental toxicity. No effects by THFMA were found on the fertility index and on the number of implantations.

Based on the adverse effects observed on gestational length and the pregnancy outcome, RAC concludes that a classification of THFMA for sexual function and fertility in category 2 (Repr. 2, H360f) is warranted.

RAC notes that the database with regards to THFMA and reproductive toxicity is limited. Further, with regards to lack of information on a potential mechanism, a similar remark was made by RAC in the case of THFA. In that case, RAC concluded that a **classification as Repr 1B; H360Df is warranted**.

Additional references

BAUA report. Geier J & Schuber S (2021). Frequency of skin sensitisation to specific substances and in specific occupational groups. DOI: 10.21934/baua:bericht20210122

Consumer Product Information Database (checked April 2023). https://www.whatsinproducts.com/chemicals/view/1/303/002455-24-5/Tetrahydrofurfuryl%20methacrylate

ECHA (2012). RAC Opinion proposing harmonised classification and labelling at EU level of tetrahydrofurfuryl alcohol; tetrahydro-2-furylmethanol https://chemicalsinourlife.echa.europa.eu/documents/10162/214b71f2-578b-20df-cc4b-04bbb5e2bfca

ECHA (2012). CLH report of tetrahydrofurfuryl alcohol. https://chemicalsinourlife.echa.europa.eu/documents/10162/6e55e3e9-12e3-6f56-fb43-f4084795ccaa

Heratizadeh A et al. (2021). Contact sensitization in dental technicians with occupational contact dermatitis. Data of the Information Network of Departments of Dermatology (IVDK) 2001–2015. Contact Dermatitis, 78, 266–273. doi:10.1111/cod.12943

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).