Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling at EU level of

tris(2-methoxyethoxy)vinylsilane; 6-(2-methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane

EC Number: 213-934-0
CAS Number: 1067-53-4

CLH-O-0000001412-86-207/F

Adopted

8 June 2018

8 June 2018

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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: tris(2-methoxyethoxy)vinylsilane; 6-(2-methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane

EC Number: 213-934-0

CAS Number: 1067-53-4

The proposal was submitted by Austria and received by RAC on 31 May 2017.

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 20 June 2017. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 4 August 2017.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

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 2018 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 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	tris(2-methoxyethoxy)vinylsilane	213-934-0	1067-53-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
RAC opinion	TBD	tris(2-methoxyethoxy)vinylsilane; 6-(2-methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane	213-934-0	1067-53-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by COM	TBD	tris(2-methoxyethoxy)vinylsilane; 6-(2-methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane	213-934-0	1067-53-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Although there are no *in vivo* studies available on the metabolism of tris(2-methoxyethoxy)vinylsilane in mammals, a well-conducted *in vitro* hydrolysis study (GLP compliant, OECD TG 111) demonstrated fast and effective hydrolysis of the parent compound to 2-methoxyethanol and vinylsilanetriol at physiological pH values. It may be assumed that this hydrolysis also takes place *in vivo* in mammals, especially under acidic conditions of the stomach (ECHA, 2012; 2016; OECD, 2006). This hydrolysis step is relevant for the hazardous properties of tris(2-methoxyethoxy)vinylsilane because of the inherent toxicological properties of 2-methoxyethanol, a substance with a harmonised classification in the CLP Regulation as Repr. 1B for fertility and developmental toxicity. However, from the results of structure activity relationship analysis presented by the dossier submitter (DS) in the background document, it may not be excluded that tris(2-methoxyethoxy)vinylsilane is also metabolised via other pathways. Therefore, quantitative conclusions on the relevance of 2-methoxyethanol as a critical metabolite for the classification of tris(2-methoxyethoxy)vinylsilane are not possible.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Tris(2-methoxyethoxy)vinylsilane was negative in three reverse bacterial mutation assays (Ames assays), in one mammalian chromosome aberration test *in vitro* on Chinese hamster ovary cells and in one mammalian cell gene mutation test with mouse lymphoma L5178Y cells. All the tests were performed according to Good Laboratory Practices (GLP), followed OECD test guidelines (TG) or were of acceptable quality.

The Dossier Submitter (DS) noted that ambiguous effects with respect to germ cell mutagenicity have been observed with the substance 2-methoxyethanol (WHO, 2009), which is a probable metabolite of tris(2-methoxyethoxy)vinylsilane. 2-Methoxyethanol does not induce gene mutations in *in vitro* investigations. However, there is some indication that it induces clastogenic damage and there is consistent evidence that the initial metabolite 2-methoxyacetaldehyde (MALD) is genotoxic *in vitro* in several cell lines. Results of the available *in vivo* studies suggest that 2-methoxyethanol is not genotoxic in somatic cells. Although there has been some suggestions of an induction of genetic effects in male germ cells, the results from these studies are inconclusive (WHO, 2009). Also, the Drexler and Hartwig, 2009 considered that the majority of *in vitro* investigations and animal studies do not indicate genotoxic effects or germ cell toxicity for 2-methoxyethanol. In agreement with this evaluation, the substance does not have a harmonised classification according to CLP Regulation (EC) No. 1272/2008 (Annex VI) for this endpoint.

Based on these data, the DS concluded that tris(2-methoxyethoxy)vinylsilane does not warrant classification for germ cell mutagenicity.

Comments received during public consultation

Three Member States Competent Authorities (MSCAs) supported no classification of Tris(2-methoxyethoxy)vinylsilane as a germ cell mutagen.

Assessment and comparison with the classification criteria

According to Annex VI of the CLP regulation, classification in germ cell mutagenicity Category 2 is based on "positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from:

- Somatic cell mutagenicity tests *in vivo*, in mammals; or

- Other *in vivo* somatic genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assay"

Taking into account negative results in several *in vitro* studies, RAC is of the opinion that tris(2-methoxyethoxy)vinylsilane does not warrant classification for germ cell mutagenicity.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The potential adverse effects of tris(2-methoxyethoxy)vinylsilane on sexual function and fertility and on development were assessed based on results of a combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test performed according to OECD TG 422 and performed under GLP. In this study, CD(SD) rats (10/sex/group) were given 0, 25, 175 and 250mg/kg bw/d by gavage. Males were exposed to tris(2-methoxyethoxy)vinylsilane during 14 days prior to mating and throughout the mating period of 14 days. Females were exposed to the test substance during the toxicity phase of 28 days. In the reproductive screening phase, other groups of females were administered tris(2-methoxyethoxy)vinylsilane by gavage daily for a minimum of 14 days prior to mating, throughout mating and gestation and continuing through lactation day 3. Since the original study report was not available to the DS, qualitative descriptions of results were taken by the DS from the Reach registration section of the ECHA dissemination website.

According to the DS, exposure to tris(2-methoxyethoxy)vinylsilane did not result in marked systemic toxicity at any dose level. There were no clinical findings reported in males and females during the toxicity phase and all animals survived until study termination up to 250 mg/kg bw/d. There were no test article-related effects observed at the functional observation battery (FOB) or locomotor activity evaluations in the males or during the toxicity phase of the females at any dose level. In the high dose males, food consumption was reduced in the first week of dosing, body weight gain was lowered in the third and fourth week and on day 28 body weight was 6.7% lower than in control males. These parameters were not affected in females during the toxicity phase. Body weight gain and food consumption (only during gestation but not during the premating phase) was reduced in the reproductive screening phase, treated females at GD20 had a mean body weight 22.1% lower than in control dams. The latter finding was attributed to total resorption in five of nine dams.

Effect on sexual function and fertility

According to the DS, the study provided evidence of adverse effects on reproduction in male and in female rats as demonstrated by, e.g., reduced fertility index, seminiferous tubule degeneration, hypospermia and prostate atrophy (males) or reduced fertility and changes in gestational length (females).

At a dose of 250 mg/kg bw in males, the following effects were observed: the mean number of days between pairing and coitus was increased; the mean absolute and relative testes and epididymal weights were reduced; microscopally, small/soft testes correlated with seminiferous tubule degeneration in all males; hypospermia and luminal cellular debris in epididymides (secondary to loss of spermatogenesis in testes); mean absolute and relative prostate weights were reduced. In females exposed at a dose of 250 mg/kg/d, 9 of 10 females were with evidence of mating, but fertility index was 60% vs. 90% in the control group. In addition, 3 out of 9 reproductive screening phase females mated were found non-gravidae and the mean gestation length was increased in the single female that delivered.

At a dose of 75 mg/kg in males, mean absolute and relative prostate weights were reduced. This reduction correlated microscopically with decreased secretion and/or atrophy of the prostate. In females, the mean gestation length was increased, and 1 moribund female was euthanised in extremis, probably due to dystocia (GD 22).

The NOAEL for reproductive effects (25 mg/kg bw/d) is equal or lower than the NOAEL for other systemic endpoints (75 mg/kg bw/d in females; 25 mg/kg bw/d in males). The reproductive toxicity does not appear to be unspecific or secondary effects from general toxicity.

The DS also reported similar effects observed from exposure of rats to 2-methoxyethanol in numerous experimental studies (WHO, 2009). 2-Methoxyethanol is an assumed metabolite of tris(2-methoxyethoxy)vinylsilane, formed by hydrolysis. In the subacute rat oral toxicity study by Chapin et al. (1985), 2-methoxyethanol caused reduced fertility in males at a dose level of 200 mg/kg/d. At dose levels of 200 and 100 mg/kg bw/d, 2-methoxyethanol produced widespread testicular damage and elevations of abnormal sperm forms in epididymis. At 50 mg/kg bw/d, very mild testicular effects at 50 mg/kg bw/d were observed. Percentage of females found pregnant after mating and number of live fetuses per pregnant female after mating with exposed males was reduced at 200 mg/kg bw/d and 100 mg/kg bw/d, but not at 50 mg/kg bw/d.

According to the DS, the study of Chapin et al. (1985) with 2-methoxyethanol provides supportive evidence that tris(2-methoxyethoxy)vinylsilane causes reproductive effects, although quantitative conclusions (compatibility of effect doses for tris(2-methoxyethoxy)vinylsilane and for 2-methoxyethanol) cannot be provided.

Based on the above data, the DS proposed to classify tris(2-methoxyethoxy)vinylsilane as Repr. 1B; H360F (May damage fertility).

Developmental toxicity

Developmental toxicity was assessed by the DS based on effects observed in the combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats described above.

At a dose level of 250 mg/kg/d, in 5 out of 9 females the litters were entirely resorbed and total litter loss was observed in 1 out of 9 pregnant females at lactation day 0. The number of resorptions and total number of preimplantation loss per female was significantly elevated.

At a dose level of 75 kg/kg/d postnatal survival was reduced shortly after birth due to:

- total litter loss in 1 female at lactation day 2
- mean number of pups born and alive on PND 0 was reduced (due to slight increase in number of pups dead, missing and presumed cannibalised)
- mean number of implantation sites reduced,

- number of unaccounted for implantation sites increased, which most probably was due to increased number of preimplantation loss.

No developmental effects were found at dose of 25 mg/kg/d.

In summary, exposure to tris(2-methoxyethoxy)vinylsilane during pregnancy of rats leads to increased resorptions, litter losses and reduced implantations at doses not causing a marked maternal toxicity. There have been no adequate examinations on (skeletal or visceral) malformations on the fetus or postpartum. This uncertainty is due to the screening type of the study design (OECD guideline 422). No adequate study according to OECD TG 414 is available.

According to the DS, it is known that 2-methoxyethanol is a developmental toxicant classified as Repr. 1B; H360FD. Developmental effects have been observed from exposure of rats to 2-methoxyethanol in numerous experimental studies (WHO, 2009). The study by Nelson et al. (1989) on 2-methoxyethanol is used as a key study in the REACH registration dossier to demonstrate the developmental toxicity of 2-methoxyethanol.

Based on the above data DS proposed to classify tris(2-methoxyethoxy)vinylsilane as Repr. 1B; H360D May damage the unborn child.

Comments received during public consultation

Three MSCAs supported classification of tris(2-methoxyethoxy)vinylsilane as Repr. 1B; H360FD.

Assessment and comparison with the classification criteria

Classification as Repr. 1A is not warranted because of the lack of human data.

Sexual Function and Fertility

Regarding adverse effects on reproductive function and fertility, in the rat combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test there were clear treatment-related adverse effects on fertility or reproductive performance from a dose level of 75 mg/kg bw/day. RAC agrees with the DS that the study provided clear evidence of adverse effects on reproduction in male and in female rats as demonstrated by reduced fertility index, seminiferous tubule degeneration, hypospermia and prostate atrophy (males) or reduced fertility and changes in gestational length (females).

The same study also provided clear evidence for significant developmental effects associated with tris(2-methoxyethoxy)vinylsilane from a dose level of 75 mg/kg bw/day. There was no indication of malformations but the number of resorptions and the total number of preimplantation loss per female was significantly elevated.

In conclusion, taking into account the clear evidence derived from an acceptable animal study that tris(2-methoxyethoxy)vinylsilane is affecting spermatogenesis, reduces the fertility index, leads to increased preimplantation loss, increased intrauterine deaths of embryo and foetuses, increased mortality of newborn rats shortly after birth at dose levels not causing marked parental toxicity, RAC agrees with the DS that tris(2-methoxyethoxy)vinylsilane warrants classification as Repr. 1B; H360FD (May damage fertility; may damage the unborn child).

Such classification is further supported by the fact that 2-methoxyethanol, a product of tris(2-methoxyethoxy)vinylsilane hydrolysis, and a presumed metabolite of tris(2-methoxyethoxy)vinylsilane in mammals is a known reproductive toxicant with harmonised classification as Repr. 1B; H360FD.

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).