Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling
at EU level of

Bis(2-(2-methoxyethoxy)ethyl)ether; tetraglyme

EC Number: 205-594-7
CAS Number: 143-24-8

CLH-O-0000001412-86-215/F

Adopted

8 June 2018

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8 June 2018

CLH-O-0000001412-86-215/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: Bis(2-(2-methoxyethoxy)ethyl)ether; tetraglyme

EC Number: 205-594-7

CAS Number: 143-24-8

The proposal was submitted by Austria and received by RAC on 26 July 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 13 September 2017. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 30 October 2017.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Daniel Borg

Co-Rapporteur, appointed by RAC: Betty Hakkert

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	603-RST-VW-Y	bis(2-(2-methoxyethoxy)ethyl) ether; tetraglyme	205-594-7	143-24-8	Repr. 1B	H360	GHS08 Dgr	H360			
RAC opinion	603-RST-VW-Y	bis(2-(2-methoxyethoxy)ethyl) ether; tetraglyme	205-594-7	143-24-8	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by COM	603-RST-VW-Y	bis(2-(2-methoxyethoxy)ethyl) ether; tetraglyme	205-594-7	143-24-8	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Bis(2-(2-methoxyethoxy)ethyl)ether, also named tetraethylene glycol dimethyl ether (TEGDME) or tetraglyme (used herein) is an organic, colourless aprotic solvent with high chemical and thermal stability. It is used in e.g. paints and coatings as well as in separation processes and high temperature reactions.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) proposed to classify tetraglyme as Repr. 1B, H360. Their proposal was based on read-across from the other glymes (mono-, di- and triglyme), as well as their assumed common metabolites 2-methoxyethanol (2-ME) and 2-methoxyacetic acid (MAA), supported by adverse effects on fertility and development of tetraglyme in two dose range finding studies and one repeated dose toxicity study in rats. The studies on the target substance tetraglyme were used by the DS to verify that exposure to tetraglyme leads to 'glyme-specific' toxicity, thereby providing scientific justification for the read-across approach. Glymes, which consist of repetitive ethylene glycol units, are known to cause testis toxicity and developmental toxicity. Mono-, di- and triglyme, as well as 2-ME and MAA all have a harmonised classification in Annex VI to the CLP Regulation as Repr. 1B (see Tables below).

Dossier submitter's justification of read-across and characterisation of the category approach (according to the ECHA Read-Across Assessment Framework, RAAF[1])

The chemical structures of the glymes are similar and consists of an ethylene glycol ether chain methylated at the terminal positions. The DS rationale for the read-across is that the target chemical tetraglyme belongs to the homologous series of glymes which form a "chain length category" with an increasing number of CH_2CH_2O units. Tetraglyme has the longest chain length of these, with four ethylene glycol units, while the source substances tri-, di-, and monoglyme have, three, two and one ethylene glycol units, respectively (Table below).

The DS assumed that the target substance tetraglyme and the source substances (mono-, di-, and triglyme and the metabolites 2-ME and MAA) share the same toxic mode of action. This corresponds to the RAAF scenarios 3 and 4.

[1] http://echa.europa.eu/support/grouping-of-substances-and-read-across

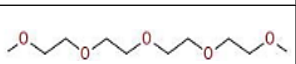
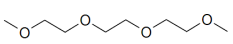
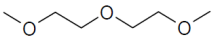
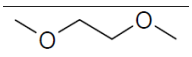
RAAF Scenario 3, Category approach: *(Bio)transformation to common compound(s): Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on a worst-case approach.*

No toxicokinetic data were available for tetraglyme. However, toxicokinetic data for diglyme demonstrated the formation 2-ME and MAA. When the DS applied the OECD QSAR Toolbox (rat liver S9 metabolism simulator) on tetraglyme, triglyme, diglyme and monoglyme, formation of MAA (as well as other oxy-, carboxy-, and hydroxy metabolites of the glyme structure) was suggested for all substances. The DS assumed that increasing chain lengths could slightly slow down bioavailability or metabolism, leading to reduced potency of the higher chain length variants.

RAAF Scenario 4, Category approach: Different compounds have the same type of effect(s). Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on a worst-case approach.

The table below contains a summary of studies and effects as well as classification under CLP relevant for the classification proposal of the target substance tetraglyme and other glymes (source substances) provided by the DS.

Table. Summary of relevant studies and effects and classification under CLP relevant for this classification proposal and for the target substance tetraglyme and its source substances. This table is a modification of Table Table B. 4.10.3.4 from the CLH report).

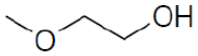
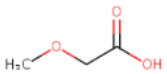
	Target substance	Source substances (other glymes)		
Substance	Tetraglyme	Triglyme	Diglyme	Monoglyme
Structure				
Harmonised C&L under CLP	Proposed by the DS as: Repr. 1B; H360 without F/f or D/d	Repr 1B. H360fD	Repr. 1B; H360FD	Repr. 1B; H360FD
Repeated Dose Toxicity				
Subacute	Rat oral 28d (OECD 407, GLP). (0, 62.5, 250, 1000 mg/kg/d, Purity 99.9%, 5/sex/group) LOAEL/NOAEL: 1000/250 mg/kg/d. Absolute/ relative (Abs/rel.) testis wt -13%/-10%, degradation of germinal epithelium and single cell necrosis with associated decreased mature sperm counts (2/5).	Rat oral 28d (OECD 407, GLP). LOAEL/ NOAEL: 1000/250 mg/kg/d. Rel testis wt -52%), ↓ testis size, ↓ epididymis wt, necrosis of germinal epithelium, oligospermia and azoospermia.	Rat oral 20d. LOAEL < 684 mg/kg/d. ↓ abs/rel. testis wt, marked degenerative changes, ↓ LDH-X activity, ↓epididymis wt. Rat respiratory 2 wks (OECD 412). LOAEC/ NOAEC: 370/110 ppm. ↓ prostate wt, ↓ seminal vesicle wt, ↓ testis wt, atrophy of testes/epididymis/ seminal vesicle/ prostate, ↓ spermatogenesis.	Mouse oral 5 wks. LOAEL < 250 mg/kg/d. ↓ rel. testis wt, atrophy of seminiferous epithelium, ↓ combined wt of seminal vesicles and coagulating gland.

Reproductive/developmental toxicity				
Fertility	Rat reproductive/ developmental (repro/dev.) tox dose-range finding study (OECD 421). 0, 250, 500, 1000 mg/kg/d, Purity 99.3%, 3/sex/group) Male F0 LOAEL/ NOAEL: 1000/500 mg/kg/d. Rel. testis wt -40%, rel. epididymis wt -30%. No general toxicity. Female F0 LOAEL/ NOAEL: 500/250 mg/kg/d. Prolonged gestation, 1 dam with stillborn pups. No general toxicity except (non-adjusted) ↓ bw gain at 1000 mg/kg/d. F1 LOAEL/NOAEL: 500/ 250 mg/kg/d. Post implantation (impl.) loss: 23%/100% at 500/1000 mg/kg/d. No general toxicity.	Mouse continuous breeding study with cross-over mating Male F0 LOAEL/ NOAEL: 1470/830 mg/kg/d. ↑ liver weight Female F0 LOAEL/ NOAEL: 1470/830 mg/kg/d: ↓ fertility, F1 LOAEL/NOAEL: 1470/830 mg/kg/d: ↓ live pups/litter (6 vs 12 (control), ↓ litters/pair	Rat dominant lethal test (inhalation). LOAEL/NOAEL: 1000/250 ppm. ↓ pregnancy rates, ↑ pre- and post-impl. loss, ↓ male fertility	No data.
Developmental toxicity	Rat dev. tox dose-range finding study (OECD 414). 0, 250, 500, 1000 mg/kg/d, Purity 99.3%, 7-8 females/group) LOAEL (maternal tox): >1000 mg/kg/d. LOAEL (dev.tox): ≤ 250 mg/kg/d. ↑ post-impl. loss (14.7%/96.8% at 500/1000 mg/kg/d). ↓ mean litter weight ↑ malformations from 250 mg/kg/d, e.g.: - Forepaw: absent 4th metacarpal - Hindpaw: absent phalanges - 4th sternebrum absent	Rabbit dev. tox study (OECD 414). LOAEL (maternal tox.): > 250 mg/kg/d. LOAEL/NOAEL (dev. Tox.): 125/75 mg/kg/d. ↑ prenatal mortality/litter > 175 mg/kg/d: ↑ malformations - Missing toenails, - Microdactyly - Ectrodactyly - small spleen	Rabbit dev. tox study (OECD 414). LOAEL/NOAEL (maternal tox): 175/100 mg/kg/d. ↑ mortality LOAEL/NOAEL (dev. tox): 50/25 mg/kg/d. ↓ prenatal growth and viability, ↑ malformations (axial skeleton, kidney, spleen, cardiovascular).	Rat dev. tox study LOAEL/NOAEL (maternal tox.): 250/120 mg/kg/d: ↓ body weight LOAEL/NOAEL (dev. tox): < 30 mg/kg bw/d. ↓ live birth, edema. 60 mg/kg/: ↑ resorptions, ↓ live births, edema, ↓ growth

	- Hyoid absent - Xiphoid absent - Supraoccipital bone absent - Heart: enlarged ventricle (L/R) - Small thymus	Mouse dev. tox study (OECD 414). LOAEL (maternal tox.): 1000 mg/kg/d. LOAEL/NOAEL (dev.tox): 500/250 mg/kg/d. ↑ post-impl. loss, ↓ fetal bw, ↑ malformations (neuronal tube, cranio-facial structures, axial skeleton).	Mouse dev. tox study LOAEL (maternal tox.): >500 mg/kg /d LOAEL (dev. tox.): 62.5 mg/kg/d. ↓ fetal bw/litter, ↓ live fetuses. 125 mg/kg/d: ↑ dead fetuses/ litter. ≥ 250 mg/kg/d: embryotoxicity, malformations (exencephaly, fore- and hindlimbs)	Mouse dev. tox study. LOAEL (maternal tox.) > 490 mg/kg/d LOAEL/NOAEL (dev. tox): < 250 mg/kg/d: ↑ malformations (fused ribs, vertebrae) >350 mg/kg/d: ↑ gross malformations (exencephaly, caudal defect, umbilical hernia).

The table below contains the classifications under CLP for the metabolites 2-ME and MAA (source substances).

Table. Classification under CLP for the source substances 2-ME and MAA relevant for this classification proposal

	Source chemicals (metabolites)	
Chemical name	2-Methoxyethanol (2-ME)	Methoxyacetic acid (MAA)
Structure		
C&L under CLP	Repr. 1B; H360 FD	Repr. 1B; H360FD

The two dose-range finding studies on tetraglyme show adverse effects on fertility and development without any apparent maternal toxicity and effects on testes were also observed in a 28-day study. However, the DS does not propose further f/F or d/D specification for the following reasons: 1) tetraglyme seems less potent compared to the other glymes; 2) uncertainties related to testing, data documentation and read across, 3) the reasons for classification of the other glymes are not entirely clear; and 4) inconsistency of the classification under the previous regulation with the current CLP regulation (monoglyme). The DS considers the category approach for read-across of relevant properties to be sufficiently robust for classification of tetraglyme for reproductive toxicity in category 1B, H360, supported by the studies on tetraglyme itself.

Comments received during public consultation

Nine comments were received in total. All four member states (MS) commenting supported classification for Repr. 1B. In several comments the issue whether f/F and d/D specification should be added was raised. Two MS considered the data on tetraglyme itself sufficient for classification as Repr. 1B, H360FD, and questioned the DS proposal not to suggest a further specification. One MS considered classification as Repr. 1B, H360FD possible, based on data for tetraglyme in combination with read-across from the source substances. One member state

supported Repr. 1B for development but requested additional information (the basis for classification of triglyme as Repr. 2 for fertility) in order to conclude on cat 1B or 2 for effects on fertility. The DS responded that arguments for not further specifying the classification have been provided and that it is up to RAC to decide whether a further differentiation is possible. One MS asked for additional quantitative metabolism data that would improve the assessment. The DS responded that no such additional metabolism data are available.

An OECD 422-study on tetraglyme that was not part of the classification proposal was submitted by industry. Based on the results, the study established a parental NOAEL of 100 mg/kg. The reproduction and developmental NOAEL was derived as 300 mg/kg.

RAC acknowledges the effects described. However, RAC disagrees with the industry's view that the effects would be severe enough to cause secondary effects on fertility and development. Thus, RAC considers the clear effects on fertility and development at 1000 mg/kg bw/day, noted already at 300 mg/kg bw/day, to be relevant for classification.

Assessment and comparison with the classification criteria

RAC evaluation of the category approach (read-across)

The DS has applied a read-across approach corresponding to scenarios 3 and 4 in the ECHA read-across assessment framework (RAAF). Key elements included demonstration of a similar chemical structure and chemical properties, similar breakdown products and similar toxicity profiles.

RAAF Scenario 3 - (Bio)transformation to common compound(s)

Of the glymes presented in the CLH report, experimental data on metabolism (*in vivo*/*in vitro*) is available only for diglyme. The data show that the main pathway of biotransformation of diglyme involves cleavage of the central ether bond which result in formation of 2-methoxyethanol (2-ME) which is subsequently oxidised to methoxyacetic acid (MAA). No experimental data are available for the other glymes. The OECD QSAR Toolbox suggested that they had similar metabolic pathways resulting in the formation of 2-ME and MAA for all four glymes. This is supported by the similar toxicological profiles of mono-, di-, tri and tetraglyme (see RAAF scenario 4 below). The formation of the metabolite MAA has in a previous evaluation by industry been considered a prerequisite for the effects of glymes on testes and development (ECETOC, 2005).

RAAF Scenario 4 - Different compounds have the same type of effect(s)

Ethylene-based glymes (such as mono-, di-, tri and tetraglyme) are known to cause testicular atrophy and developmental toxicity (ECETOC, 2005).

The repeated dose toxicity studies show similar effects for the glymes (Table "Summary of relevant studies and effects and classification under CLP" above + the industry study submitted at PC). With regard to reproductive organs, the common effects consist of reduced testis weights combined with degeneration of germinal epithelium in the seminiferous tubules. For tetraglyme, triglyme and diglyme associated effects on spermatogenesis were also reported. In addition, effects on epididymis weights were documented for tetraglyme, triglyme and diglyme as well as effects on the seminal vesicles of monoglyme, diglyme and triglyme. The effects of glymes on testes and other reproductive organs are likely mediated via the metabolite MAA, as stated by the DS in the BD and in other evaluations (e.g. ECETOC, 2005). Metabolism studies in rats following exposure to diglyme show that MAA constitute approximately 6% of the administered

dose after 96h. MAA is a potent testicular toxicant with reduced testis weight (~10%) observed already after a single dose of 50 mg/kg bw/day (Spano *et al*., 1991).

The reproductive toxicity studies also show effects on male fertility (Table "Summary of relevant studies and effects and classification under CLP" above + the industry study submitted at PC). For tetraglyme, reduced testis and epididymis weight was seen in the reproductive screening study, while for diglyme reduced male fertility was reported, which may be a result of the reduced testis and epididymis weight/function (not evaluated in the study). In females, increased post implantation losses and reduction of viable pups was observed. Although litter loss and decreased pup viability are rather non-specific forms of reproductive/developmental toxicity the findings in these studies are considered supportive, but not conclusive, for a similar toxicity pattern between the glymes.

The developmental toxicity studies show, in addition to increased post-implantation losses and decreased pup viability, a range of structural malformation and anomalies in e.g. skeletal and cranio-facial structures. Altogether the findings in the repeated dose- and the reproductive and developmental toxicity studies are considered supportive for a similar toxicity pattern between the glymes.

Summary of RAC's evaluation of read-across

Overall, RAC considers that the key aspects required for read-across of relevant properties from mono-, di, and triglyme to tetraglyme are fulfilled based on the combination of RAAF scenarios 3 and 4. The results from repeated dosing and reproductive/developmental toxicity studies and similar harmonised classifications provide sufficient evidence to conclude that glymes share a similar toxicity pattern (RAAF scenario 4), likely mediated via the common potent metabolite MAA (RAAF scenario 3). However, RAC acknowledges the difficulties in specifying d/D and f/F based on the read-across. In the present case there are however some studies available with tetraglyme, e.g. range findings studies and a reproductive/ developmental toxicity screening study that do provide additional information for further specification.

RAC evaluation of effects by tetraglyme on fertility

The reproductive/developmental toxicity dose-range finding study (OECD 421) and the combined repeated dose toxicity study with reproductive/developmental toxicity screening (OECD 422, GLP) provided by industry as well as the 28-day repeated dose study (OECD 407) show adverse effects of tetraglyme on fertility and sexual function in rats without any significant general toxicity.

In the OECD 421-study, significantly reduced testis weights (-40%) and epididymis weights (-30%) were observed in F0 males at 1000 mg/kg bw/day (Table "Summary of relevant studies and effects and classification under CLP" above). No clinical signs of toxicity were observed and body weights were similar between treated and control animals.

In the OECD 422-study, significantly reduced testis weights (-50%) and epididymis weights (-30%) were observed at 1000 mg/kg bw/day (Table " Absolute organ weights in male Wistar rats", above). Marked bilateral seminiferous tubular degeneration (with associated depletion of germ cells) was reported in the testes and in the epididymides slight to moderate hypospermia was reported in 9/9 examined males. At 300 mg/kg bw/day 2/10 males showed abnormalities in their sexual organs and the females mating with these males did not give birth to any pups. In the females, decreased numbers of corpora lutea and implantation sites were observed at 300 and 1000 mg/kg bw/day (Table " Effects on reproductive parameters in female Wistar rats", above) and at 1000 mg/kg bw/day the mean mating time was increased to 4.7 days compared to 2.5 days in the other dose groups.

In the OECD 407-study, decreased testis weight (absolute -13%/relative -10%) was observed at 1000 mg/kg bw/day (Table "Summary of relevant studies and effects and classification under

CLP" above). In 2/5 males, degradation of germinal epithelium and single cell necrosis with associated decreased mature sperm counts were observed.

Overall RAC considers the effects on the male reproductive organs toxicologically significant. Effects were observed at or below the limit dose of 1000 mg/kg bw/day. Small but significant effects occurred at 500 mg/kg bw/day in the OECD 421-study and fertility related findings were evident in 2/10 pairs at 300 mg/kg bw/day in the full OECD 422-study. The more severe and pronounced effects occurred at the limit dose, but RAC considers these effects occurring at and below the limit dose to be relevant for classification. This is further supported by the following:

- Several of the studies were screening/range-finding studies with few animals and thus low statistical power. Higher-tier studies may have picked up statistically significant effects at lower concentrations.
- The likely metabolism of tetraglyme to MAA and similar toxicity seen with other glymes. The classification of triglyme in Cat. 2 for fertility was considered a borderline case and was partly based on data from another species (mouse). The mouse may be less sensitive than the rat, which has been the model species used for tetraglyme.
- Humans are more sensitive to hypospermia than rats.

Therefore, based on all the above considerations, RAC concludes that tetraglyme should be classified in category 1B for effects on fertility (Repr. 1B H360F).

RAC evaluation of effects of tetraglyme on development

The reproductive/developmental toxicity and the prenatal developmental toxicity dose-range finding studies (OECD 421 and OECD414) as well as the combined repeated dose toxicity study with reproductive/developmental toxicity screening (OECD 422, GLP) provided by industry all show adverse effects of tetraglyme on development in rats in the absence of any significant maternal toxicity.

In the OECD 421-study, significantly increased post-implantation losses occurred in F1 at 500 and 1000 mg/kg bw/day (23% and 100% vs 10.5% in controls). No general toxicity was reported, except a decreased bw gain at 1000 mg/kg bw/day (not adjusted for uterus weight) which was assumed to be due to the litter losses.

In the OECD 414-study, significantly increased post-implantation losses as well as decreased pup weight and viability were observed at 500 and 1000 mg/kg bw/day (14.5% and 96.8% vs 5.7% in controls). Adjusted maternal body weights were similar between dosed and control animals. At ≥ 250 mg/kg bw/day, increased external, soft tissue and skeletal malformations were observed (Table below).

Table. Incidences of foetal malformation in Wistar rats following in-utero exposure to tetraglyme (OECD 414)

	Control			250 mg/kg bw			500 mg/kg bw		
Number of foetuses/litters examined*	42/7			40/7			28/5		
	A	B	C	A	B	C	A	B	C
Absent - hyoid bone	0	0	0	3	8	1	14	50	5
Absent - xiphoid bone	0	0	0	12	30	4	21	75	4
Absent - 4th metacarpal in forepaws	4	10	4	22	55	6	19	68	5
Absent - hindpaw phalanges	5	12	3	25	63	6	16	57	4
Absent - 4th sternebrae	6	14	4	3	8	2	14	50	5
Number of foetuses/litters examined*	39/8			36/6			41/8		
	A	B	C	A	B	C	A	B	C
Heart enlarged ventricle (L)	0	0	0	0	0	0	2	5	2
Heart enlarged ventricle (R)	1	3	1	2	6	1	3	7	2
Small thymus	0	0	0	0	0	0	2	5	2

A - Total incidences for the particular abnormality; B - % incidence; C - Number of litters in the group having at least one foetus with the particular abnormality. * - One half of each litter was examined for skeletal alterations the remaining litter was examined for soft tissue abnormalities

RAC notes that significant developmental effects were seen below the limit dose in the absence of parental toxicity, including in screening studies with lower statistical power than higher-tier studies. Also, similar developmental effects have been seen in studies with the other glymes. RAC considers the effects observed following exposure to tetraglyme itself sufficient to warrant further classification for effects on development (D).

RAC evaluation of concentration limits

From the information provided by the DS, RAC considers that tetraglyme is of medium potency and therefore no specific concentration limit is necessary. RAC notes that the effects on fertility and development were mainly observed at concentrations ≥ 250 mg/kg bw/day tetraglyme. Additionally, the dose range finding studies provide insufficient evidence on the potency of tetraglyme to allow derivation of specific concentration limits because of the limited number of animals used in these studies.

RAC conclusion

RAC is of the opinion that tetraglyme should be classified as Repr. 1B H360FD without any specific concentration limits. This opinion is based on the data on tetraglyme itself and was supported by read-across data from the other glymes as well as their assumed common metabolites.

Additional references

ECB (2002). Summary Record – Meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances. ECB Ispra, 5 – 7 September 2001. ECBI/58/01 – Rev. 4. 18, July 2002.

ECETOC (2005). The Toxicology of Glycol Ethers and its Relevance to Man (Fourth Edition) Volume I.

Spano M. *et al.* (1991). Evaluation of 2-methoxyacetic acid toxicity on mouse germ cells by flow cytometry. J. Toxicol. Environ.Health 34(1): 157-176.

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).