Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1A OR 1B, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): Methoxyacetic acid (MAA)

EC Number(s): 210-894-6

CAS Number(s): 625-45-6

Submitted by: **Swedish Chemicals Agency,**

August 2012

CONTENTS

TABLES

LIST OF ABBREVIATIONS

ABP	Androgen Binding Protein
AR	Androgen Receptor
CAT	Chloramphenicol Acetyl Transferase
CLP	Classification, Labeling, Packaging
CMR	Carcinogenic, Mutagenic or toxic to Reproduction
DEGDME	Diethylene Glycol Dimethylether
DHT	Dihydrotestosterone
DMEP	2-Dimethoxyethylphtalate
DNEL	Derived No Effect Level
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment Tool
ED	Endocrine Disruptor
EGDME	Ethylene Glycol Dimethylether
EGEE	2-Ethoxyethanol
EGME	2-Methoxyethanol
EGMEA	2-Methoxyethanol Acetate
ER	Estrogen Receptor
ESR	Existing Substances Regulation
GA	Glycolic Acid
HDAC	Histone Deacetylase
HPVC	High Production Volumes Chemical
IOELV	Indicative Occupational Exposure Limit Value
LCM	Laser Capture Microdissection
LPVC	Low Production Volume Chemical
MAA	2-Methoxyacetic Acid
MAPK	Mitogen-Activated Protein Kinase
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
NR	Nuclear Receptor
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
OSPA	Oxygenated Solvents Producers Association
PBT	Persistent, Bioaccumulative and Toxic
PPE	Personal Protective Equipment
PR	Progesterone Receptor
RACB	Reproductive Assessment by Continuous Breeding (NTP study protocol)
RAR	Retinoic Acid Receptor
RT-PCR	Real Time Reverse-Transcriptase Polymerase Chain Reaction

vPvB	Very Persistent, and Very Bioaccumulative
SPIN	Substances in Preparations in Nordic Countries
SVHC	Substance of Very High Concern
TEGDME	Triethylene Glycol Dimethyl Ether
TR	Thyroid Hormone Receptor
TUNEL	In Situ Labeling of Fragmented DNA
WB	Western Blot

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Substance Name(s): Methoxyacetic acid

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- The substance is proposed to be identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 1B.
- It is proposed to identify the substance as substance of equivalent concern according to Article 57 (f).

Summary of how the substance meets the CMR (Cat 1A or 1B), PBT or vPvB criteria, or is considered to be a substance giving rise to an equivalent level of concern

Methoxyacetic acid (MAA) is listed as entry 607-312-00-1 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008[1] as toxic for reproduction (1B). This corresponds to a classification in Annex VI, part 3, Table 3.2 of Regulation (EC) No 1272/2008 (the list of harmonized classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) as toxic to reproduction, category 2. This classification of the substance in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

Methoxyacetic acid (MAA) is proposed to be identified as a substance of very high concern because of its endocrine disrupting properties and scientific evidence of probable serious effects to human health and the environment, which give rise to equivalent level of concern according to Article 57 (f) of Regulation (EC) 1907/2006 (REACH).

The proposal is based on the following findings:

1) MAA is an endocrine disruptor. It fulfills the criteria of scenario A according to the OECD draft guidance document for endocrine disruptors (OECD GD 150[2]). Specifically:

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

[2] ENV/JM/TG(2012) GUIDANCE DOCUMENT ON STANDARDISED TEST GUIDELINES FOR EVALUATING CHEMICALS FOR ENDOCRINE DISRUPTION

a) MAA effects observed in *in vitro* assays (OECD level 2) provide mechanistic data supporting an endocrine mediated mode of action. Estrogenic and androgenic modulatory responses have been reported.

b) MAA effects observed in *in vivo* assays (OECD level 3) provide data about selected mechanisms and pathways that are endocrine mediated: Estrogen and androgen receptors expression were altered (up-regulated) in rat testis in a spermatocyte apoptosis model. Anti-estrogenic and progesterone modulatory responses have been reported in mice uteri.

c) MAA effects observed in *in vivo* assays (OECD level 4) providing data on adverse effects on endocrine-relevant endpoints after treatment with metabolic precursor of MAA, ethylene glycol monomethyl ether (EGME) include: effects on rat female fertility (estrous cyclicity, progesterone levels, histopatological changes in the ovaries) and developmental toxicity (fetotoxicity in rats, mice and rabbits). It has been established that MAA is an active metabolite of EGME.

d) MAA effects observed in an *in vivo* assay (OECD level 5) providing more comprehensive data on adverse effects on endocrine-relevant endpoints over more extensive parts of the life cycle of the organism, i.e. a two-generation NTP study of MAA in mice, showed severely affected fertility in males and females and increased number of dead and resorbed fetuses.

2) The inherent endocrine disrupting property of MAA gives rise to equivalent level of concern.

a) The effects on fertility and fetal development are severe and irreversible, affecting fundamental parts of human life which contribute to the general societal concern for these kinds of effects.

b) Since numerous mammals are part of the environment a similar degree of concern applies also for the environment.

c) Furthermore there is uncertainty associated with assessing safe exposure levels for endocrine disrupting substances. It is not clear whether threshold levels can be established for all hormone-mediated adverse effects and it is therefore considered necessary that ED properties and the associated uncertainty in risk assessment are reflected in the risk management of this group of substances.

In conclusion and taking into account all available information on the intrinsic endocrine disrupting properties of MAA and its adverse effects, it is concluded that MAA is a substance for which there is scientific evidence of probable serious effects to humans and the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

Registration (s) submitted for the substance:

Yes

PART I -

JUSTIFICATION

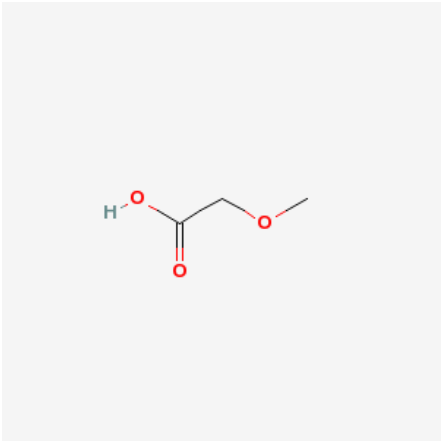
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1. Substance identity

EC number:	**210-894-6**
EC name:	methoxyacetic acid
CAS number (in the EC inventory):	**625-45-6**
CAS number:	**625-45-6**
CAS name:	Acetic acid, 2-methoxy-
IUPAC name:	2-Methoxyacetic acid
Index number in Annex VI of the CLP Regulation	607-312-00-1
Molecular formula:	$C_3H_6O_3$
Molecular weight range:	90.08 g/mol

Structural formula:



1.2 Composition of the substance

Name: methoxyacetic acid

Description: -

Degree of purity: > 98 % (w/w)

Table 2. Constituents

Constituents	Typical concentration	Concentration range	Remarks
methoxyacetic acid 210-894-6	*see Confidential Annex*	*see Confidential Annex*	

Table 3. Impurities

Impurities	Typical concentration	Concentration range	Remarks
see confidential Annex	*see Confidential Annex*		

1.3 Physico-chemical properties

Table 4. Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	Colourless liquid with pungent odour	*from registration**
Melting/freezing point	7 °C 8 °C 7-9 °C	*from registration**
Boiling point	202°C at 1013hPa 203 °C at 1013hPa 202-204°C at 1013hPa	*from registration**
Vapour pressure	1hPa at 20°C 1.8 hPa at 20°C 4.8 hPa at 50°C	*from registration**
Water solubility	completely miscible	*from registration**
Partition coefficient n-octanol/water (log value)	log Pow: -0.68	*from registration**

*From dissemination database according to Regulation (EC) No.1907/2006, article 119.

2 HARMONISED CLASSIFICATION AND LABELLING

Methoxyacetic acid is classified and labelled according to Reg (EC) 1272/2008, Annex VI, Table 3.1 and Table 3.2, as follows (see Table 5 and 6):

Table 5. Classification of MAA according to Reg (EC) 1272/2008, Annex VI, Table 3.1.

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling		Spec. Conc. Limits, Mfactors
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram Signal Word Code(s)	Hazard statement code(s)	
607-312-00-1	methoxyacetic acid	210-894-6	625-45-6	Repr. 1B Acute Tox. 4 Skin Corr. 1B	H360FD H302 H314	GHS08 GHS05 GHS07 Dgr		STOT SE 3; H335: C ≥ 5 %

Table 6. Classification of MAA according to Reg (EC) 1272/2008, Annex VI, Table 3.2.

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Conc. Limits
607-312-00-1	methoxyacetic acid	210-894-6	625-45-6	Repr. Cat. 2; R60-61 Xn; R22 C; R34	T R: 60-61-22-34 S: 53-45	C; R34: C ≥ 10 % Xi; R36/37/38: 5 % ≤ C < 10 %

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier. For short summary see Annex I, section 11.2.

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 1.2 on Harmonised Classification and Labelling, section 4.1 on endocrine disrupting properties and for supplementary data Annex I, section 11.1.

4.1 Endocrine disrupting properties

MAA is listed on the TEDX List of Potential Endocrine Disruptors[3].

Within the work on this dossier the assessment of studies concerning MAA ED effects has been performed. The quality (reliability and relevance) of the studies not considered in previous assessments was assessed using the categories according to Klimisch et al., 1997 and the OECD recommended studies as a reference (see Table 7). The relevance of some of the effects observed in *in vitro* studies with the use of cotransfection models with exogenous receptors (Tirado et al., 2004; Jansen et al., 2004; Bagchi et al., 2009) was considered uncertain for *in vivo* responses. This is in light of the recent report showing that in such systems up-regulatory effects were observed due to MAA activation of promotors CMV, pRL-tk, pRL-SV40 that are commonly used in transfection

[3] http://www.endocrinedisruption.com/endocrine.TEDXList.overview.php

techniques, leading to effects that may not be in concordance with *in vivo* biological responses (Henley et al., 2009).

For the overview of the studies concerning MAA ED mode of action and effects see Table 8. Studies have been categorized according to the OECD conceptual framework assay level (OECD/ENV/JM/TG (2012).

A body of scientific evidence exist concerning the effect of MAA on receptors and/or signaling relevant for endocrine systems including androgenic signaling (Tirado et al., 2003; Bagchi et al., 2009, 2011), estrogenic signaling (Tirado et al., 2004; Jansen et al., 2004; Henley et al. 2009, 2010) and the molecular mechanisms involved (Jansen et al., 2004). The review paper (Tabb and Blumberg, 2006) on different modes of action for endocrine-disrupting chemicals listed MAA (and EGME) in the group of so called hormone sensitizers including short-chain fatty acids that alter hormonal receptors activity by effect on protein kinases or histone deacetylases.

Anti-estrogenic effect of MAA has been shown *in vitro* and *in vivo* (Henley et al. 2009, 2010). Henley et al., 2009 investigated effects of MAA on the estrogen signaling pathway with the rationale that this pathway is necessary for normal reproductive function and modulates gene expression. These studies evaluated the mechanistic effects of MAA on estrogen receptor (ER) expression and estrogen signaling using *in vitro* and *in vivo* model systems. *In vitro* experiments on mammalian cell culture MCF-7 showed that treatment with MAA in concentrations 1-20 mM for 24h decreased endogenous ERalpha expression (both protein levels and mRNA) and that this resulted in disrupted ERalpha mediated signaling, as MAA attenuated the estrogen-induced responses in gene expression. Authors concluded that MAA disrupts estrogen receptor (ER) signaling through a mechanism that involves decreased endogenous ERalpha expression and that these results are consistent with reproductive toxicities associated with exposure to a metabolic precursor of MAA, EGME. This is not a standard OECD test and corresponds to level 2 "*in vitro* assays providing mechanistic data". It needs to be noted that within the proposed battery of tests there is no test aiming at investigating the mechanism of action connected to the influence of the level of the ER. The analysis of the quality of the study resulted in the judgment that this study is reliable and relevant. The *in vitro* effects were further investigated *in vivo* in ovariectomized mice treated i.p. with 400 mg/kg for 2 h before necropsy (Henley et al., 2009). Changes included about 30% decreased relative expression of ERalpha and effects on estrogen-modulated gene expression in uterine tissue of MAA pre-treated mice. Those changes however did not reach statistical significance. This is not a standard OECD study. The relevance and reliability of this study has been assessed using reference to the standard OECD TG 440 study - uterotrophic bioassay in rodents. Both are short term *in vivo* screening assays in female rodents for chemicals that interact with the ER and investigate effects elicited in animal models where endogenous estrogen levels are minimal. In the standard OECD study the endpoint "increase in uterine weight (or uterotrophic response)" is recommended. In the assessed study the relative expression of ERalpha and the estrogen-modulated gene expression in uterine tissue are the measured endpoints. The studied endpoints are assessed to be relevant for studying MAA specific mode of action. The standard study endpoint "uterine weight" has been criticized for low sensitivity (Kortenkamp et al., 2011) and the relevance for only limited types of mode of action (OECD, ENV/JM/TG (2012). The i.p. route of administration in the assessed study diverges from the relevant human exposure routes. However, many studies on toxicokinetics with oral or inhalatory exposure to MAA and metabolic precursors like EGME show systemic distribution with concentrations in fetuses higher than maternal. This study corresponds to level 3 of the OECD framework for testing of EDs "*In vivo* assays providing data about single endocrine mechanisms and effects". As the observed effects were not statistically significant the results are considered equivocal and the study as supportive in the weight of evidence. Further effects associated with estrogen system, like changes in estrous cyclicity, histo-pathological

changes in the ovaries were observed in a study with rats administered with MAA precursor EGME (Davis et al., 1997).

There is evidence that for male reproduction, including testicular development and spermatogenesis, both androgenic and estrogenic regulation is critical. It has been shown that MAA caused stage specific up and down regulation of AR expression in pachytene spermatocytes in rat testis (Tirado 2003) and up-regulation of ERbeta in rat testis (Tirado 2004); those are studies corresponding to level 3 of the OECD conceptual framework. The results of the studies on the reproductive and developmental effects of MAA and metabolic precursor EGME (see Table 8 and for supplementary information paragraph 11.1) present the evidence corresponding to levels 4 and 5 of the OECD conceptual framework (OECD/ENV/JM/TG (2012).

The effects of MAA on the expression of hormonal receptors is not only limited to AR and ER. Enhancement of transcriptional efficacy of ligand activated nuclear receptor PR responsive gene calcitonin in immature mice uteri has been also reported (Jansen et al., 2004).

In conclusion, MAA is considered an endocrine disrupting chemical fulfilling the criteria of scenario A according to OECD GD 150[4].

Specifically, *in vitro* studies representing level 2 of the OECD conceptual framework indicate that MAA affects the transcriptional mechanisms of nuclear receptors including AR and ER, and modulates estrogenic and androgenic responsive gene expressions. *In vivo* studies corresponding to level 3 of the OECD conceptual framework confirm effects on the expression levels of ER and AR and modulation of ER and PR responsive genes. Specifically, estrogen and androgen receptors expression were altered (up-regulated) in rat testis in a spermatocyte apoptosis model. Anti-estrogenic and progesterone modulatory responses have been reported in mice uteri. At the level 4-5 OECD conceptual framework studies reported adverse health effects associated to estrogenic and androgenic disturbances, like female and male reproductive toxicity and foetal developmental toxicity. Treatment with metabolic precursor of MAA, ethylene glycol monomethyl ether (EGME) affected rat female fertility (estrous cyclicity, progesterone levels, histopatological changes in the ovaries) and developmental toxicity (fetotoxicity in rats, mice and rabbits). It has been established that MAA is an active metabolite of EGME. A two-generation NTP study of MAA in mice showed severely affected fertility in males and females and increased number of dead and resorbed fetuses.

[4] ENV/JM/TG(2012) GUIDANCE DOCUMENT ON STANDARDISED TEST GUIDELINES FOR EVALUATING CHEMICALS FOR ENDOCRINE DISRUPTION

Table 7 Evaluation of the studies concerning MAA ED effects and their quality according to Klimisch et al., 1997 categories.

***In vivo* study**	**Categories of reliability *In vivo* study[5]**	**Hanley et al., 1984ab**	**NTP, 1986 Abstract RACB84103**	**Davis et al., 1997**	**Tirado et al., 2003**	**Tirado et al., 2004**	**Jansen et al., 2004**		**Henley et al., 2009**	
	Information on the test animals	OECD 414, Conclusion based on the previous risk assessments ECETOC 2005 WHO, 2009	RACB protocol, Conclusion based on the previous risk assessments ECETOC 2005	Reliable – Conclusion based on the previous risk assessments ECETOC 2005	YES Sprague-Dawley rats, weight 400 g	YES Sprague-Dawley rats, weight 400 g	YES Female immature (21-day-old) CD-1 mice; 30-week-old C57BL/6 mice		YES Ten-week-old ovariectomized C57BL/6 mice	
	Purity, composition, origin of the test substance				NO/YES[6]				NO/YES [32]	
	Number of animals				YES N=5 for most of the groups; One group with N=3	Yes N = 3-6/group	YES N=5		Yes N = 3	
	Scope of the investigations per animal (and description of the methods)				YES MAA induced apoptosis in pachytene spermatocytes (TUNEL) Cyclic expression of AR protein in testis (Immunohistochemistry) AR and Androgen Binding Protein (ABP) mRNA levels in whole testis (RT-PCR) AR and ABP mRNA levels in stage-specific tubules (LCM).	YES MAA induced apoptosis in pachytene spermatocytes (TUNEL) ERbeta mRNA in unseparated testicular cells and isolated germ cells (RT-PCR, LCM); ERbeta levels (immuno-detection in pachytene	YES Effect of MAA on the expression of calcitonin mRNA level in uteri (RT-PCR).		YES Effect of MAA on ERalpha mRNA level in uteri; effect of MAA on estrogen-modulated gene expression in uteri (RT-PCR).	

[5] Klimisch et al., 1997.

[6] No purity provided but assumed as origin from well established chemicals supplier

						spermatocytes, WB of cytosolic and nuclear fractions of testicular extracts).				
	Description of the changes observed				YES MAA treatment led to: All pachytene spermatocytes at stages II-IV and XII became TUNEL positive (but no at stages V-IX); Alternation in the expression of the AR in Sertoli cells, both increase and decrease dependent on the cell developmental stage; Overall AR mRNA levels in testis did not change; AR mRNA levels were affected in seminiferous tubules in all stages (decrease in VII-VIII, increase in II-IV and X-XIII); Correlation of changes in AR mRNA and proteins levels with 3h lag-phase.	YES MAA treatment led to: Stage specific positive TUNEL reaction of pachytene spermatocytes (maximal in stages X-XIII); Increase of ERbeta mRNA in unseparated testicular cells; ERbeta immunostaining in pachytene spermatocytes in stages X-XIII corresponding to increased apoptosis; Up-regulation of ERbeta protein in cytoplasm in testicular extracts; Up regulation of ERbeta mRNA in LCM captured seminiferous tubules.	YES Enhancement of the transcriptional efficacy of ligand activated nuclear hormone receptors by up to 8-fold. Calcitonin gene expression was elevated only when the mice were treated with combination of MAA and PR agonist R5020.		YES 30% decrease of ERalpha mRNA (not statistically significant); pretreatment with MAA reduced the E2-mediated stimulation of tested genes (not statistically significant).	
	Control group				YES	YES	YES		YES	
	Description of the test conditions				YES	YES	YES		YES	

	Description of the route and doses of administration				YES Single dose i.p. injection 650 mg/kg bw	YES Single dose i.p. injection 650 mg/kg bw	YES Single dose i.p. injection 400 mg/kg		YES Single dose i.p. injection 400 mg/kg	
	Dose or concentration relationship if possible				NO	NO	NO		NO	
	CONCLUSSION	**Reliable / relevant**	**Reliable / relevant**	**Reliable / relevant**	**Reliable / relevant**	**Reliable / relevant**	**Reliable / relevant**	-	**Reliable / relevant**	-
***In vitro* study**	**Categories of reliability *In vitro* study[32]**				**Tirado et al., 2003**	**Tirado et al., 2004**	**Jansen et al., 2004**	**Bagchi et al., 2009**	**Henley et al., 2009**	**Bagchi et al., 2011**
	Description of the test system and test method in details				YES Sertoli Cell Lines MSC-1 and TM4; Fibroblast cell line L929 stably transfected with androgen-inducible construct MMTV-CAT and probasin-luciferase; WB analysis; CAT and Luciferase Assay.	YES Human hepatoma HepG2 cells stably cotransfected with ERbeta-responsive element containing pCMV-beta-galactosidase and a Luciferase reporter system.	YES Human hepatoma HepG2 cells cotransfected with ERbeta-responsive element containing pCMV-beta-galactosidase and a Luciferase reporter system; Human breast cancer cell expressing progesterone receptor PR - T47D cells.	YES HEK293(tsA201), TM3 mouse Leydig cells, TM4 mouse Sertoli cells, HepG2; Transfected with receptor plasmids either AR, ERalpha, ERbeta, TRbeta, PR-B, RARalpha, RARbeta,, RARgamma; MAA effect on activation of those receptors was analyzed using reporter assay.	YES HeLa cells transiently transfected with either ERalpha or ERbeta expression vector containing a CMV promotor; MCF-7 cells with endogenous ERalpha; RNA analysis (RT-PCR); Protein analysis (WB).	YES Mouse TM3 Leydig cell stably expressing human AR cDNA (retroviral infection); Microarray analysis.
	Purity, composition, origin of the test substance				NO/YES [32]					
	Description of the effects studied				Direct effects of MAA on the expression of AR and ABP mRNA and proteins in Sertoli cell lines – increases of ABP were observed; no effect on AR mRNA or protein level;	MAA at 5mM activated the ERbeta equally to estradiol at 1 nM.	Ability to enhance the transcriptional efficacy of the ERbeta-estradiol complex (additional tests on	MAA potentiated the AR response without altering the EC50 for androgen responsiveness; In TM3 mouse testicular Leydig cells de-regulated	MAA potentiated the activity of E2 in HeLa cells transfected with ER expression system. Effect	Impact of MAA on AR responsive gene expression by global transcriptional profiling; MAA at 5mM

			L929 cells expressing endogenous AR and stably transfected with a MMTV promoter-CAT reporter system or with a probasin promotor-luciferase reporter construct exposed to MAA in the presence or absence of androgens – MAA showed no androgenic activity of its own, but at 5mM it potentiated the effects of dihydrotestosterone (DHT) 2 to 4 times and the effect is AR receptor dependent.		ERalpha and TRbeta and AR); MAA at 5mM potentiated the 17-beta-estradiol-mediated activation of ERbeta transcriptional activity (30- vs 230-fold induction) Effect not specific to ERbeta, tests with other receptors positive too. In T47D cells MAA potentiated the agonist induced activity of endogenous PR-mediated activity by 2-fold. Further mechanistic effects investigated.	(both up and down regulation) genes involved in androgen synthesis.	mediated by increase of exogenous human ER expression via transactivation of the CMV promoter by MAA; MAA transactivated other promoters too; MAA treatment reduced endogenous ERalpha expression in MCF-7 cells.	altered the expression of a large number of testosterone-responsive genes, many examples of both stimulatory and inhibitory interactions between MAA and testosterone.
	Data on the dose or concentration		YES 0.1 - 5 mM	YES 0.1 - 5 mM	YES 5 mM	YES 5 mM	YES 1 - 20 mM	YES 5 mM
	Data on secondary effects which may influence a result		NO	NO	NO	NO	YES interference of MAA with testing system analyzed	NO
	Appropriate negative and positive controls as integral parts of the test		YES	YES	YES	YES	YES	YES
	References on adequacy		YES	YES/NO			YES	YES

	of the method should be given or generally known		Scientifically established methods	Scientifically established methods Relevance of the effects *in vitro* cotransfection models for *in vivo* is uncertain in light of the report by Henley 2009 on the MAA transactivation of promotors CMV, pRL-tk, pRL-SV40 that are commonly used in transfection techniques.	Scientifically established methods	Scientifically established methods
	CONCLUSSION		**Reliable / relevant**	**Reliable / relevance uncertain**	**Reliable / relevant**	**Reliable / relevant**

Table 8 Overview of studies concerning MAA ED modes of action and human health effects according to Assay levels of OECD Conceptual Framework

Type of study	**Investigated effects and results**	**Reliability and relevance (see table 10)**		**Reference**	**Assay level**
In vitro Mouse fibroblast expressing endogenous AR transfected with AR promoter reporter systems	Testing of MAA ability to potentiate DHT activation of AR. Observed: MAA did not activate AR directly, it did potentiate DHT activation of the AR by 2- to 4-fold.	reliable	relevant	Tirado et al., 2003	**Level 2**[7]
In vitro HepG2 cells co-transfected with ERbeta and a reporter system	MAA activation of ERbeta. Estrogenic activation.	reliable	uncertain[8]	Tirado et al., 2004	
In vitro Human hepatic carcinoma (HepG2) cells transfected with estrogen-responsive reporter gene with ERbeta expression plasmid	Enhancement of the transcriptional efficacy of the ERbeta-estradiol complex. MAA potentiated the 17-b-estradiol-mediated activation of ERbeta transcriptional activity in ERE reporter (30 v 230 fold). Response blocked by antiestrogen indicated receptor-dependent mechanism. Analogical effects observed in others nuclear receptors including TRbeta, AR. The mitogen-activated protein kinase (MAPK) signaling pathway is involved in MAA mediated potentiation of nuclear receptor (NR) transcriptional activity.	reliable	uncertain[34]	Jansen et al., 2004	
In vitro	Inhibition of histone deacetylase HDAC, effects on	reliable	relevant	Jansen et al., 2004	

[7]OECD Conceptual Framework Level 2: In Vitro Assays Providing Data About Selected Endocrine Mechanism(s) / Pathway(s)

[8] Relevance of the effects *in vitro* cotransfection models for *in vivo* is uncertain in light of the report by Henley 2009 on the MAA transactivation of promotors CMV, pRL-tk, pRL-SV40 that are commonly used in transfection techniques (see Table 10).

HeLa cells	endogenous histone acetylation				
In vitro HEK293(tsA201) transfected with plasmids expressing human AR, human ERalpha, ERbeta, TR beta, RARs and reporter plasmid	MAA (5mM) enhanced transcriptional activity of AR, ERalpha, ERbeta and TRbeta -activated receptors, but not RARs.	reliable	uncertain[34]	Bagchi et al., 2009	
In vitro TM3 Mouse Leydig cells and TM4 Sertoli cells	MAA-induced potentiation of AR activity observed in TM3 but not TM4, only observed in cells transfected with exogenous AR.	reliable	uncertain – only observed in transfected exogenous AR	Bagchi et al., 2009	
In vitro MCF-7 cells	Decreased endogenous ERalpha expression Attenuation of E2-stimulated endogenous gene expression.	reliable	relevant	Henley et al., 2009	
In vitro HeLa cells transiently transfected with human ERalpha or ERbeta vector containing a cytomegalovirus CMV promotor	Potentiation of 17b-estradiol (E2) stimulation of a estrogen-responsive reporter plasmid.	reliable	uncertain Increased exogenous ER expression due to MAA mediated activation of the CMV promoter	Henley et al., 2009	
In vitro Mouse TM3 Leydig cell line stably expressing androgen receptor (TM3-AR)	MAA impact androgen-responsive genes using transcriptional profiling MAA enhanced and/or antagonized androgenic responses.	reliable	relevant	Bagchi et al., 2011	
In vivo Male rats treated with MAA, single i.p. injection 650 mg/kg bw, Model of pachytene spermatocyte apoptosis	Testing of MAA effect on stage-specific expression of AR protein in Sertoli cells. Observed: In MAA-treated rats higher AR expression was found in Sertoli cells coincident with the MAA-induced apoptosis of late-stage pachytene spermatocytes. Androgen binding protein (ABP) mRNA levels were altered in a stage-specific manner.	reliable	relevant	Tirado et al., 2003	**Level 3**[9]
In vivo Male rats treated with MAA, single i.p. injection 650 mg/kg bw, Model of pachytene spermatocyte apoptosis	Participation of ERbeta during the apoptosis prior germ cell loss. Observed increase of ERbeta mRNA in germ cell fractions and testis, and ERbeta protein in the cytoplasm of pachytene spermatocytes of afflicted tubules.	reliable	relevant	Tirado et al., 2004	

[9] OECD Conceptual Framework Level 3: In Vivo Assays Providing Data about Selected Endocrine Mechanism(s) / Pathway(s)

In vivo Immature CD-1 mice, single dose i.p. injection 400 mg/kg bw	Effect of MAA on progesterone-regulated gene expression in uteri. Up-regulation of calcitonin mRNA after combinatory exposure to MAA and R5020.	reliable	relevant	Jansen et al., 2004	
In vivo Ovariectomised C57BL/6 mice, single dose i.p. injection 400 mg/kg bw	Decreased endogenous ERalpha expression in uteri, attenuation of E2-stimulated endogenous gene expression; effects did not reach statistical significance – supportive study.	reliable	relevant however effects did not reach statistical significance – supportive study	Henley et al. 2009	
In vivo EGME (metabolic precursor of MAA) administered to rats, repeated daily doses 10, 100 and 300 mg/kg body weight	Endpoints: estrous cyclicity, vaginal cytology and histology, ovarian histology, serum hormones. Changes in estrous cyclicity, progesterone levels, histo-pathological changes in the ovaries in rats administered 100 and 300 mg/kg body weight per day or more in repeated doses, NOAEL 10 mg/kg body weight per day.	reliable	relevant	Davis et al., 1997.	**Level 4**[10]
In vivo OECD 414, EGME (metabolic precursor of MAA), inhalatory repeated maternal exposure, doses differed for different species and ranged: 0, 3, (rats and rabbits only), 10 (all) and 50 ppm (all) (0, 10, 32, 160 mg/ m^3)	Developmental toxicity effects at concentrations of 50 ppm (160 mg/m^3) and above in all species: slight fetotoxicity in rats and mice at this dose (no effects below); in rabbits malformations in essentially all organ systems in majority of foetuses (arthrogryposis, digit and ventral wall defects, ventricular septal defects, renal defects, skeletal defects. In rabbits there was statistically significant increase in the delay of ossification of sternebrae (in relation to the actual, but not the historical control) at 10 ppm (32 mg/m^3). No developmental effects were observed at 3 ppm (9 mg/ m^3). WHO (2009) derived NOAEC 10 ppm (32 mg/m^3) for developmental effect (although slight effects on the blood parameters and ossification delay were seen). ECETOC (2005) based on delay of ossification considered the level of 10 ppm (32 mg/m^3) of EGME as an effect level. INRS reported EGME NOAEC 3 ppm (10 mg/m^3)	reliable	relevant	Hanley et al., 1984ab WHO, 2009 ECETOC 2005	

[10] OECD Conceptual Framework Level 4: In Vivo Assays Providing Data on Adverse Effects on Endocrine-Relevant Endpoints

	based on the effects for rabbit.				
In vivo 2-generation NTP continuous breeding study, Swiss CD-1 mice, RACB protocol, (20/sex/group), MAA via the drinking water for 98 days at doses of 140, 240 or 390 mg MAA/kg bw/d.	Severe effects on fertility and pup survival were observed at all doses. No NOAEL could be established.	reliable	relevant	Abstract RACB84103 ECETOC, 2005 and the references therein NTP, 1986; Chapin and Sloane, 1997.	**Level 5[11]:**
review	Modes of action for ED chemicals, categorized MAA as a hormone sensitizer based on Jansen 2004; Tirado 2003, 2004.	-	-	Tabb and Blumberg, 2006	Not applicable; Review on ED mode of action
review	Mode of actions of ED chemicals, categorized MAA to ER signaling disruptors through the mechanism that involves decreased endogenous ERalpha expression based on Henley et al 2009.	-	-	Henley et al. 2010	

[11]OECD Conceptual Framework Level 5: In Vivo Assays Providing More Comprehensive Data on Adverse Effects on Endocrine-Relevant Endpoints Over More Extensive Parts of the Life Cycle of the Organism

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier. For short summary see Annex I, section 11.2.

Considering the ED properties the results from the studies on ED properties, section 4.1, are considered relevant for the environment, in particular for mammals.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 CMR assessment

Methoxyacetic acid (MAA) is listed as entry 607-312-00-1 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008[12] as toxic for reproduction (1B). This corresponds to a classification in Annex VI, part 3, Table 3.2 of Regulation (EC) No 1272/2008 (the list of harmonized classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) as toxic to reproduction, category 2.

This classification of the substance(s) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

6.2 Equivalent level of concern assessment

Methoxyacetic acid (MAA) is proposed to be identified as a substance of very high concern because of its endocrine disrupting properties and scientific evidence of probable serious effects to human health and the environment, which give rise to equivalent level of concern according to Article 57 (f) of Regulation (EC) 1907/2006 (REACH).

The proposal is based on the following findings:

3) MAA is an endocrine disruptor. It fulfills the criteria of scenario A according to the OECD draft guidance document for endocrine disruptors (OECD GD 150[13]). Specifically:

   a) MAA effects observed in *in vitro* assays (OECD level 2) provide mechanistic data supporting an endocrine mediated mode of action. Estrogenic and androgenic modulatory responses have been reported.

   b) MAA effects observed in *in vivo* assays (OECD level 3) provide data about selected mechanisms and pathways that are endocrine mediated: Estrogen and androgen receptors

[12] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC,
and amending Regulation (EC) No 1907/2006.

[13] ENV/JM/TG(2012) GUIDANCE DOCUMENT ON STANDARDISED TEST GUIDELINES FOR EVALUATING CHEMICALS FOR ENDOCRINE DISRUPTION

expression were altered (up-regulated) in rat testis in a spermatocyte apoptosis model. Anti-estrogenic and progesterone modulatory responses have been reported in mice uteri.

c) MAA effects observed in *in vivo* assays (OECD level 4) providing data on adverse effects on endocrine-relevant endpoints after treatment with metabolic precursor of MAA, ethylene glycol monomethyl ether (EGME) include: effects on rat female fertility (estrous cyclicity, progesterone levels, histopatological changes in the ovaries) and developmental toxicity (fetotoxicity in rats, mice and rabbits). It has been established that MAA is an active metabolite of EGME.

d) MAA effects observed in an *in vivo* assay (OECD level 5), providing more comprehensive data on adverse effects on endocrine-relevant endpoints over more extensive parts of the life cycle of the organism, i.e. a two-generation NTP study of MAA in mice, showed severely affected fertility in males and females and increased number of dead and resorbed fetuses.

4) The inherent endocrine disrupting property of MAA gives rise to equivalent level of concern.

d) The effects on fertility and fetal development are severe and irreversible, affecting fundamental parts of human life which contribute to the general societal concern for these kinds of effects.

e) Since numerous mammals are part of the environment a similar degree of concern applies also for the environment.

f) Furthermore there is uncertainty associated with assessing safe exposure levels for endocrine disrupting substances. It is not clear whether threshold levels can be established for all hormone-mediated adverse effects and it is therefore considered necessary that ED properties and the associated uncertainty in risk assessment are reflected in the risk management of this group of substances.

In conclusion and taking into account all available information on the intrinsic endocrine disrupting properties of MAA and its adverse effects, it is concluded that MAA is a substance for which there is scientific evidence of probable serious effects to humans and the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

Part II - INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

7 INFORMATION ON EXPOSURE

7.1 Information on volumes

7.1.1 Information from ESR, REACH registration(s) and CLP notification(s)

MAA was not listed in any of the priority lists of the former Existing Substances Regulation (ESR) program on the evaluation and control of the risks of existing substances under Council Regulation (EEC) No 793/93[14]. It was reported to be a low production volume chemical (LPVC)[15] under the ESR program.

The current REACH based information indicates high production volumes HPV of MAA (registered for intermediate use only).

The CLP inventory listed 145 classification notifiers[16].

For more information please see the confidential Annex, 7.5.

7.1.2 Information from Product Register Data

The Swedish product register database and the Nordic SPIN (Norway, Sweden, Finland and Denmark) database indicate that the substance has been present as such or in mixtures used in industrial applications e.g. detergents. However it is likely that in these cases MAA is present as an impurity as it occurs together with glycolic acid (GA) and the concentrations are low.

Trends that could be observed when analysing the total volume of MAA reported in the SPIN database over the period of 2001 – 2009 (Table 8), indicated stable volumes in Sweden slightly more than 0.5 tonne, with slowly increasing number of preparations from 9 to 24, decreasing volumes in Denmark from 1.8 tonnes to 0.8, but increasing number of preparations from 18 to 42, the data for Norway was only available for 2008-2009 and the volumes reported were higher and increasing 2.8-3.5 tonnes, with moderate number of preparations. The data reported for Finland indicated no use of the substance.

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[14] Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances

[15] placed on the market in volumes between 10 tonnes and 1000 tonnes per year per producer/importer

[16] CL inventory database http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 6th of March 2012)

Data in the Swedish product register that covers years 1992 – 2009 indicates use of products which contain the substance. For the number of products and total amount of MAA in products for the years 1999-2009, see Table 9. Very few products were registered as available to consumers before 2007 and no products directly available to consumers were reported in 2008-2009. The most recent data indicate industrial uses in branches like cleaning activities and industry for fabricated metal products. The products containing MAA were for example detergents. The concentration of MAA in the registered products in Sweden is very low (for example 0.01%) for the great majority of the products. The low concentration and the fact that the substance occurs in most of the products together with GA indicate that the substance is an impurity in GA. For a few products it is even registered as an impurity. For the other products, that information could have been missed when reporting to the products register. The relation between the two concentrations (MAA / GA) is almost the same for the other products, around 0.01% or less.

Table 9. Registration of products containing MAA in SPIN database.

year	A / P	A - Amount (tonnes) P - Number of preparations		
	Sweden	Denmark	Norway	Finland
1999	1 / 9	-	-	-
2000	1 / 12	1.8 / 18	-	-
2001	1 / 9	1.8 / 18	0	-
2002	1 / 16	1.9 / 25	0	-
2003	1 / 16	1.9 / 31	0	-
2004	1 / 15	0.8 / 29	0	-
2005	1 / 13	0.9 / 32	0	-
2006	0 / 13	0.6 / 36	0	-
2007	1 / 16	0.6 / 39	0	0
2008	1 / 19	0.6 / 44	2.8 / 6	0
2009	1 / 24	0.8 / 42	3.5 / 11	0

Table 10. Registration of products containing MAA in the Swedish products register.

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Total amount of MAA in the products (tones)	0.4	0.5	0.7	0.5	0.6	0.5	0.7	0.2	0.5	1.1	0.7
Number of products	9	9	7	16	15	15	13	14	16	19	24

7.1.3 Information from other Member States

Data in a French products register indicates that several preparations (32) containing MAA were registered within the last 10 years (2000-2010)[17].

MAA was not listed in the German exposure database MEGA[18].

7.1.4 Information on the suppliers (Internet search)

A search of the Internet revealed a moderate number of suppliers of MAA worldwide. For example a search of ChemicalBook (http://www.chemicalbook.com/) found a total of 26 suppliers in China and 39 suppliers in the rest of the world (of which 2 in Belgium, 6 in Germany, 1 in Switzerland, 5 in UK, 1 in Slovakia, and the rest outside of Europe). Similarly, ChemExper (http://www.chemexper.com/) listed a total of 96 suppliers. Most of these suppliers appear to be supplying the substance only in small quantities (laboratory-scale, up to 1 kg) but there were at least 6 suppliers listed in ChemExper supplying bulk or semi-bulk amounts (4 in China, 1 in Switzerland and 1 in UK).

7.2 Information on uses

7.2.1 Information based on REACH registration

The substance has been registered as intermediate, for use in industrial settings and under strictly controlled conditions. Process category: PROC 0: other, consumed in chemical synthesis according

[17] Contact with French Authority. Data received on the 5th of December 2011.

[18] Contact with DGUV (German Social Accident Insurance) and the information on the MEGA website

http://www.dguv.de/ifa/de/fac/reach/mega_auswertungen/index.jsp

to Article 18(4); Market sector by type of chemical product PC 19: intermediate[19]; sector of end use: SU9: Manufacture of fine chemicals[20].

For supplementary information see the confidential Annex, 7.5.

7.2.2 Information on uses based on national product registers

The search of the use category (UC62) in SPIN database indicated that the highest volumes of MAA were associated with the industrial use manufacture of chemicals and chemicals products, service to buildings and landscape activities, and category cleaning/washing agents. Other uses with low tonnage but several preparations included manufacture of food products, specialised construction activities, trade and repair of motor vehicles, and manufacture of fabricated metal product.

Data in a French products register indicates that the majority of reported 32 uses are professional uses and only one use for consumers. The indicated uses included: disinfectants (for private use), corrosive descaling agents including products for ovens and ranges, disinfectants for use on food contact surfaces, cleaning agent for ultrafiltration membranes or reverse osmosis, detergent for use on floor/wall/industrial area, products for cleaning of wheels and tyres, industrial cleaning agents, pH-regulator, anti-corrosion product.

According to Dutch information MAA is a basic chemical for the production of biocides and industrial point sources are relevant emission sources to air and water.

7.2.3 Uses identified in the patent databases

Patent database has been screened for possible MAA applications[21]. Majority of listed applications concerned synthesis of substances. Several patents included specific applications like additives for motor fuels and a fuel for internal combustion engines (1960), bleaching agent composition for housing (1993), cationic elecrocoating composition (1999), etching liquid composition (2006), pest control agent (2011).

7.2.4 Examples of professional use and consumer use products based on Internet search

Three types of uses of preparations containing MAA by consumers and / or professional users have been identified by the means of Internet search for the safety data sheets (search string “methoxyacetic acid safety data sheets”). Initial search results, over 10000 “hits” were briefly manually screened for relevant matches. The outcome is indicative of the existence of non-

[19] Transported isolated intermediate - A substance manufactured for or used for chemical processing in order to be transformed into another substance, the synthesis of which is transported between or supplied to other sites.

[20] From dissemination database according to Regulation (EC) No.1907/2006, article 119.

[21] http://depatisnet.dpma.de/DepatisNet/depatisnet?window=1&space=main&content=index&action=index&switchToLang=en

intermediate uses of MAA but should not be considered as an comprehensive list of all existing uses. Two of the three identified preparations are manufactured in Europe and one in US.

The MAA is used in a type of air freshener in a concentration below 0.5%. The product is a preparation that is a complex mixture of substances. Based on the information in the product safety data sheet the calculated concentrations of MAA in the air are expected to be below 0.06 mg/m^3 (SCA, January 2011[22]). Based on the information provided on the website of the distributor, products of this company are on the market in around 100 countries.

MAA is present in a concentration below 0.5% in a type of cleaning agent (descaler) for cleaning of cement for maintaining construction tools, equipment and vehicles. This use is mostly associated with professional applications. Products are manufactured by a French producer with global distribution to over 30 countries[23]. Products are marketed as a new generation products and safer alternative to those based on acids like hydrochloric, citric or phosphoric acid. The use is about 1 liter per 5-8 m^2. On the Swedish market the products are in the start-up phase and individual consumer use is being considered[24].

MAA is present in the concentrations 0.1 - 0.5% in the cleaning product, named bathroom disinfectant cleaner, by a producer in US (3M Company, 2010 Material Safety Data Sheet)[25].

7.2.5 Use restrictions

Consumer exposure to MAA as a substance or in preparations in concentration ≥0.5% according to DSD (from 2015 replaced by the limit ≥0.3% according to CLP) is not expected due to the restriction within Annex XVII, Appendix 6, entry 30 of REACH. The REACH restriction does not apply to articles.

The substance is regulated in two other EU directives, the Cosmetics and VOC directives. According to the Cosmetics Directive 76/768/EEC[26], Annex II, No. 674, MAA, must not form part of the composition of cosmetic products.

Due to its boiling point of 202-204 °C at 1013 hPa, MAA falls under the definition as VOC according to Directive 2004/42/EC[27] on the limitation of emissions of volatile organic compounds

[22] http://www.sca-tork.com/; Universal Airfreshener Tab Floral (Modern Fragrance) http://www.tork.co.uk/Global/2__UK_and_Ireland/United_Kingdom/6_Media%20bank/Tork%20Universal%20Air%20Freshener%20Tab%20Floral.pdf

[23] http://www.guardtechremover.com/societe-en.php

[24] contact with the Swedish distributor on the 29/02/2012

[25] http://multimedia.3m.com/mws/mediawebserver?66666UtN&ZUxL99XLxftn8TX5Vu9KcuZgVU_LXT1u666666--

[26] Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products

[27] Directive 2004/42/EC of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC

regarding the use of organic solvents in certain paints and varnishes and vehicle refinishing products.

7.2.6 Other regulatory standards

MAA is a Dutch priority substance and a (so-called) MPV-substance for which it is obligatory to minimise the emissions to air. Ad-hoc MTR (maximum allowed risk) and SW (reference) values have been derived. The Dutch indicative (temporarily) Environmental Quality Standards for Air and Water are: MTR (air): 5.96 x 10^{-3} ng/m^3; MTR (surface water): 0.692 µg/l; SW (surface water): 6.92 x 10^{-3} µg/l ; TTG (time-weighted average) during 8 hours (worker exposure): 19 mg/m^3[28].

MAA is not listed in any of three currently existing European Commission Directives establishing indicative occupational exposure limits (2000/39/EC[29], 2006/15/EC[30], 2009/161/EU[31]). It is regulated by very few nationally established limits; it is listed on the German occupational exposure limits list[32]: DFG 5 ppm or 19 mg/m^3; and Switzerland list[33] 1 ppm / 3.7 mg/m^3. Austria, Belgium, Quebec, Denmark, France, Hungary, Italy, Japan, Poland, Singapore, Spain, Sweden, The Netherlands, US NIOSH, US OSHA, UK or ACGIH have no OELs for MAA[34].

The commonly used industrial solvent ethylene glycol monomethyl ether (EGME), and the precursor of MAA, is listed in Directive 2009/161/EU with an IOELV of 1 ppm.

7.3 Results of the informal industry consultation on the manufacture and uses of MAA

Based on the lists from the REACH pre-registration, registration, CLP notification database and the open internet search over 30 companies potentially relevant for the consultation on manufacture and uses of MAA were identified and contacted.

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[28] based on the e-mail contact with Nando Goormachtigh (Nando.Goormachtigh@rivm.nl)

[29] European Commission Directive 2000/39/EC establishing a First List of Indicative Occupational Exposure Limit Values at European Community level in implementation of council directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work.

[30] European Commission Directive 2006/15/EC establishing a second list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Directives 91/322/EEC and 2000/39/EC.

[31] European Commission Directive 2009/161/EU establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC.

[32] IFA-Report 1/2011 http://publikationen.dguv.de/dguv/pdf/10002/grenzwerte2011.pdf

[33] SUVA 2011. Grenzwerte am Arbeitsplatz 2011,

https://extra.suva.ch/webshop/4E/4E20FF264EAA0450E10080000A630358.pdf

[34] Based on the e-mail contact with researchers at Royal Institute of Technology, Sweden : Linda Schenk (Linda.Schenk@abe.kth.se) and Qian Ding (Qian.Ding@abe.kth.se)

The questioner consisted of ten questions covering the activities related to MAA like: manufacture, import, uses (intermediate, industrial, professional, down stream, others) and the relevant quantities in consecutive years. Five questions related to: MAA as a substance, MAA as an impurity in other substances, mixtures containing MAA, articles containing MAA, substances metabolised or degraded to MAA. One question concerned description of applications of MAA. Two concerned possible release of MAA and human exposure, and possible environmental release, and remaining two - substitution of MAA with other substances and substitution of other substances with MAA. Template of the questioner allowed entrance of data in the structured form and as a free comments or explanatory notes. Confidentiality claims were requested to be followed in line with other data provided by industry for the REACH regulation[35].

The response ratio was about 40%. Half of the responding companies informed that they do not deal with MAA even if in the past they indicated intentions for such activities. The remaining companies confirmed any of the following: manufacturing of MAA for intermediate uses, distribution of EU produced and imported from outside of EU MAA for supported intermediate and laboratory uses, intermediate use for manufacture of other substances, non-intermediate use of MAA resulting in presence in consumer available product, the presence of MAA as an impurity in the professional use product (with the possibility to be available for consumer use).

For more specific results see the Confidential Annex.

7.4 Estimation of exposure to MAA resulting from the application of products containing low concentrations of MAA

Three exposure scenarios were calculated: two exposure scenarios for either consumer use or professional indoors use of the products containing MAA at the concentrations corresponding to the current regulatory limits of 0.5% and 0.3% have been performed with the use of ConsExpo model. 1) The first exposure scenario was based on the currently existing in EU use of air freshener; 2) The second one was the hypothetical scenario of the use of the cleaning agent. 3) Third scenario of professional use of industrial or non-industrial indoors or outdoors spraying application with a product containing below 1% MAA was calculated with ECETOC TRA.

Scenario 1: Home / institutional air freshener with MAA at concentration 0.5%.

The MAA concentration in air was calculated with ConsExpo 4.1, based on the inhalation model: exposure to vapour, constant rate and the following assumptions: exposure frequency 1/day, release duration 24 hours, applied amount 4 gram, exposure duration 24 hours, concentration of MAA 0.5%, room volume 58 m^3, ventilation rate 0.5, body weight 65 kg, inhalation uptake fraction 100%, inhalation rate 34.7 m^3/day (default, considered as a worse case).

Inhalation exposure: Inhalation mean event concentration was calculated to be 0.0263 mg/m^3. The inhalation internal dose was 0.014 mg/kg/day.

[35]The right of access to documents held by national authorities is governed by national legislation and not by EU legislation. Upon a request to read documents submitted to the authority, a check is made on a case-by-case basis and classified information according to the concerned act is blocked out. It is important to underline that Sweden´s national rules about access to information will ensure that information of the type referred to in Article 118.2 will be kept confidential when necessary and that business secrets are respected.

Scenario 2: Home or professional indoors use of cleaning product containing MAA at concentration 0.3%

The presence of MAA in cleaning products was reported. For this scenario we assumed hypothetical concentration 0.3% (equal to CLP classification limit in force from 2015).

The MAA concentration in air was calculated with ConsExpo 4.1, based on the following values: exposure frequency 1/day, application duration 20 minutes, exposure duration 8 hours, applied amount 400 g, concentration of MAA 0.3%, room volume 58 m^3, ventilation rate 0.5, release area 10 m^2, mol weight matrix 18 g/mol, mass transfer rate 0.292 m/min, body weight 65 kg, inhalation uptake fraction 100%, inhalation rate 24.1 liter/min (default, considered as a worse case), dermally exposed area 1900 cm^2, dermally applied amount 19 gram, dermal uptake fraction 100%.

Inhalation exposure: Inhalation mean event concentration was 0.474 mg/m^3, with the maximum around 1.2 mg/m^3. The inhalation internal dose was 0.084 mg/kg/day.

Dermal exposure: The dermal internal dose 0.087 mg/kg bw/d.

Combined exposure: Considering operators are exposed via the inhalation and the dermal route, combined exposure result in 0.17 mg/kg bw/d.

Scenario 3: Professional use of a concrete cleaning product containing MAA at a concentration below 1%.

The MAA concentrations in the air were calculated with ECETOC TRA (TRAM version 3) for the following scenarios: industrial spraying (PROC7) or non industrial spraying (PROC11), indoors, indoors with good ventilation, outdoors, application duration 15min -1 h, 1h – 4h, > 4h, concentration of substance in preparation <1% (the lowest from the drop down list).

Inhalation exposure: Air concentrations (8h average) were calculated and ranged between 1.4 – 7 ppm dependent on the conditions. Specifically the estimated levels were 1.4 ppm for 15 min-1h outdoors/indoors with good ventilation applications, 2 ppm for indoors application; 4.2 ppm for 1-4h outdoors/indoors with good ventilation applications, 6 ppm for indoors application; 7 ppm for > 4h outdoors/indoors with good ventilation applications.

7.5 Summary on exposure and uses

REACH registration of MAA indicates that the substance is produced in large quantities (>1000 tonnes/year/manufacturer) and used as an intermediate in industrial settings under strictly controlled conditions and closed systems for synthesis of other substances. The technical, organizational and PPE measures to minimize release and exposure are the necessary preconditions for intermediate registration under REACH.

The REACH registration does not serve as a source of information on other possible non-intermediate uses of MAA. The number of pre-registrations in REACH, members in pre-SIEF and notifications to CLP inventory indicate that the substance is relevant for a significant number of companies (> 100). The data retrieved from national databases on uses and/or exposure suggest that the substance has been and therefore still may be present in preparations with industrial uses other than intermediate, although in rather small quantities (and in some cases likely as an impurity). The open Internet search for the material/ product safety data sheets stating presence of MAA confirms

the existence of such uses with the example of a cement cleaning agent containing below 0.5% MAA.

Consumer exposure to MAA as a substance or in preparations in concentration ≥0.5%, according to DSD (from 2015 replaced by the limit ≥0.3% according to CLP) is not expected due to the restriction within Annex XVII of REACH and the ban from the use in cosmetic products due to the Cosmetics Directive. However uses below these regulatory limits have been confirmed, with the example of airfreshener containing below 0.5% on the European market or bathroom cleaning agent with 0.1-0.5% of MAA on the US market.

It needs to be emphasised that the present regulatory provisions do not provide means for gathering comprehensive data on the uses with the products containing MAA at low concentrations and below 1 tonne /year /manufacturer.

In summary, the relevant exposed groups are workers and consumers.

The intermediate use exposure is controlled by the REACH provisions for intermediates including risk managements in the form of controlled conditions and closed systems. (Workers accidental exposures are possible). The intermediate use does not fall under authorisation process.

Further workers' exposure due to non-intermediate industrial uses or presence as an impurity is expected. No data on the exposure levels have been found, so within the work on this dossier the ECETOC TRA model was used to estimate exposure during the professional use of a product containing MAA at concentration < 1%.. Estimated air concentrations ranged between 1.4 and 7 ppm (5.2 - 26 mg/m^3) depending on the use conditions. Consumers are expected to be exposed to MAA at low concentrations. Two consumers' applications containing MAA (within current regulatory limit have been identified), one in EU and the other one in US. The MAA exposure concentration due to the use of air freshener was estimated to be below 0,016 ppm (0.06 mg/m^3), based on the material safety data sheet.

8 CURRENT KNOWLEDGE ON ALTERNATIVES

Consideration of alternatives for MAA intermediate use is not relevant, as the authorization process would not affect this use.

There is limited information concerning the MAA function in the possible non-intermediate uses.

For the function as an end of life indicator[36] the alternative approaches have been identified, including examples found in patent application[37].

The function of the MAA in the identified cement cleaning agent is not clear, possibly it is present as an impurity in the substance used for manufacturing of this preparation. This product is marketed as a safer alternative to previously used products based on inorganic acids.

[36] http://wiki.answers.com/Q/Is_an_air_freshener_a_base_or_acid

[37] GB 2444702 http://www.ipo.gov.uk/p-find-publication-getPDF.pdf?PatentNo=GB2444702&DocType=A&JournalNumber=6213

9 RISK-RELATED INFORMATION

Registration as a transported isolated intermediate does not trigger requirement of chemical safety report. Consequently no exposure scenarios, no DNELs, risk assessment or CSR have been provided in the registration.

According to REACH registrations only the intermediate use under strictly controlled conditions is maintained. However non-intermediate uses potentially resulting in the exposure of workers and consumers have been identified. The estimated exposure levels from the uses of products containing low concentrations of MAA (0.3-1%) ranged from 0.007-7 ppm. Rough estimation of possible risk (see Annex I, section 11.3 and 11.4) indicated that risk may not be fully controlled.

MAA is a potent teratogen and a fertility toxicant in both male and female experimental animals. Furthermore the mode of action is associated with endocrine disrupting properties that cause additional uncertainty in the derivation of safe levels using the standard threshold approaches for risk assessment. This indicates that further regulatory action is required to control the risk of MAA.

Inclusion of MAA in the Candidate List would promote information about the existence of MAA in articles. However notification to ECHA would be limited to those articles containing MAA at a concentration above 0.1% and in quantities of MAA totaling over one tonne per year per manufacturer or importer. Information to recipients would be limited to those articles containing MAA at concentration above 0.1%. Since MAA is a volatile liquid the concentrations in articles are expected to be low.

Authorization process due to classification as toxic for reproduction (1B) according to 57 (c) would apply to the uses when the concentration of MAA is equal or above the classification of the preparation as dangerous, currently 0.5%, from 2015 limit of 0.3%. [38],[39].

Authorization process due to the properties 57(f) endocrine disrupting properties would apply to uses when the concentration limit is equal or higher than 0.1 % weight by weight (w/w). Furthermore, specific provisions concerning the authorization process could also apply later on for substances identified as 57 (f) – c.f. REACH Article 138.7

The authorization process is considered as a suitable measure to control the risks with MAA non-intermediate uses and promote their substitution by non-SVHC substances.

[38] lowest of the concentration limits specified in Directive 1999/45/EC or in Annex I to Directive 67/548/EEC

[39] REACH Article 56.6b

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11 ANNEX I – ADDITIONAL INFORMATION ON HAZARD AND RISK

11.1 Human health effects

Summarized from ECETOC (2005), WHO (2009), extended by data from publicly disseminated REACH registration dossier, and open literature search data relevant for human health with the focus on kinetic and reprotoxic effects is presented below. It supplements the data provided in chapter 4.

11.1.1 Toxikokinetics

MAA is the major metabolite of EGME and other glycol ethers like EGMEA, DEGDME, TEGDME and phthalates like 2-dimethoxyethylphtalate DMED. It appears to mediate the systemic effects of those substances with the well documented case of EGME (ECETOC, 2005 and the references therein: Miller *et al*, 1983; Gargas *et al*, 2000).

Following administration of EGME, MAA was excreted renally, partially in a conjugated form. The kinetics and metabolism studies indicated that, dependent on the dose and treatment regime, 34-65% of EGME was metabolized and excreted as MAA. There were signs of slow accumulation of MAA in non-human primates (*Macaca fascicularis*) and humans. The average half-life of MAA in humans exposed to EGME by inhalation was 77.1 hours. The concentration of MAA in embryos and in extra-embryonic fluid was 20% higher than in maternal serum in the mice studies after EGME gavage treatment (ECETOC, 2005 and the reference therein: *Miller et al., 1983b; Foster et al., 1984; Welch et al, 1988; Scott et al, 1989; Sleet et al, 1988; Groeseneken et al., 1989a; Medinsky et al., 1990; Shih et al 2000c, 2001).*

11.1.2 Repeated dose toxicity

Only short term repeated studies on MAA are available, and no sub-chronic studies have been identified. In the longest treatment study (5 weeks) the lowest tested doses of 8 mg/kg bw for 5 weeks still affected fertility of hamsters (ECETOC, 2005 and the reference therein: Peiris and Moore, 2001). In the ECETOC (2005) report it was concluded that no NOAEL for MAA could be established.

More specifically, in a rat 4 days repeated treatment study with a dose of 592 mg MAA/kg bw/d by oral gavage effects on body, liver and testis weights were observed along with degenerative histological effects in testis (ECETOC, 2005 and the reference therein: Foster et al, 1983).

In a rat 2 weeks study with 8 days treatment with doses up to 300 mg MAA/kg bw effects on thymus, testes and heamatological effects were observed with the no effect dose of 30 mg/kg bw (ECETOC, 2005 and the reference therein: Miller et al., 1982).

In the rat 28-days repeated inhalation study changes in the testes were reported and NOAEC of 60 mg/m^3 indicated, however the investigations on male fertility were considered inconclusive (ECHA dissemination and the reference therein: study report, 1994).

In a 5 weeks study on hamsters after either single doses of 0, 80, 160 or 650 mg MAA/kg bw or repeated daily doses of 0, 8, 32 or 64 mg/kg bw for 5 weeks decreased fertilization capacity was observed in all treated animals (ECETOC, 2005 and the reference therein: Peiris and Moore, 2001).

11.1.3 Toxicity for reproduction and development

Male fertility

In a large number of studies MAA was toxic to the male reproductive system in multiple species and after different routes of exposure.

MAA administered to rats or mice as single oral doses ranging from 118 to 650 mg/kg bw or an intraperitoneal (i.p.) dose of 592 mg /kg bw resulted in a significant decrease in testicular weight, histological damage or spermatocytes depletion and the lowest tested dose of 65 mg/kg bw was without effects (ECETOC, 2005 and the reference therein: Brinkworth et al, 1995; Foster 1987, 1986; Bartlett et al, 1988; Clark et al., 1997; Suter et al, 1998).

MAA administered by single i.p. injection to rats at doses higher than 60 mg/kg bw, including tested doses 300, 600 or 900 mg/kg bw, effected spermatocytes. In mice, germ cell apoptosis was observed after single i.p. injection of 650 or 1300 mg MAA/kg bw. The apoptotic mechanism could be largely prevented by treatment with calcium antagonists (ECETOC, 2005 and the reference therein: Moore et al., 1992; Krishnamurthy et al, 1998; Li et al, 1997).

Developmental effects

MAA exerts pronounced foetotoxic, embryotoxic and teratogenic effects in all species investigated (rat, mouse, rabbit, monkey and *Drosophila*) and via all routes of exposure (oral, dermal, inhalation) in the presence and absence of maternal toxicity. This has been observed in the studies with MAA and several MAA metabolic precursors like EGME, EGDME, DEGDME, TEGDME, EGMEA (ECETOC, 2005) or DMEP (Ritter et al., 1985). For MAA, critical dose levels have not yet been established but appear to be lower than those for EGME. EGME NOAEL after inhalation has been disputed to be 3 or 10 ppm (9 - 32 mg/m^3).

There are a number of studies with MAA investigating developmental effects potential. Oral single gestational treatments of rats and mice with the lowest tested doses of 180-306 mg/kg bw caused severe malformations of foetuses. This was also observed with repeated dosing of 39 or 79 mg MAA/kg bw/d during gestation in rats. Increased number of resorptions, and malformations were reported including hydronephrosis, cardiac, limb, digit, paw malformations and shortening of limbs and tails (ECETOC, 2005 and the references therein: Ritter *et al*, 1985; Sleet *et al*, 1987; Welsch *et al*, 1987; Nelson *et al*, 1989).

Sleet *et al* (1987, 1988) compared the teratogenic effects of MAA in CD-1 mice after oral and i.v. administration of 2.9 or 3.8 mmol/kg bw (260 or 340 mg/kg bw) (reviewed in ECETOC, 2005). Single i.p. injection of doses as low as 9 mg/kg bw (and up to 225 mg MAA/kg bw) during gestation of rats showed a high foetal mortality and malformations. A NOAEL was not obtained (ECETOC 2005 and the reference therein Brown *et al*, 1984).

In a 2-generation NTP continuous breeding study, mice (20/sex/group) received MAA via the drinking water for 98 days at doses of 140, 240 or 390 mg MAA/kg bw/d. Severe effects on fertility

and pups survival were observed at all doses (ECETOC, 2005 and the references therein NTP, 1986; Chapin and Sloane, 1997).

For EGME, WHO summarized developmental toxicity studies and concluded that the most informative study, the OECD 414 test of inhalatory treatment in rats, mice and rabbits (Hanley et al., 1984) derives 10 ppm (32 mg/m^3) as the NOAEC for developmental effects. The inhalatory NOAEC for EGME for developmental effects in three species (rats, mice and rabbits) was therefore established at 10 ppm (32 mg/m^3) (WHO, 2009). However ECETOC (2005) considered the level of 10 ppm (32 mg/m^3) of EGME in this study as an effects level based on results showing retarded ossifications in rabbits (in relation to the actual, but not the historical control). National Research and Safety Institute for occupational accidents prevention in France (INRS) reported EGME NOAC of 3 ppm (9 mg/m^3) based on this study (DEMETER, 2010).

11.1.4 Human data

Extensive data documenting effects on humans exist for MAA metabolic precursor EGME including effects on CNS, haematological effects, male reproductive effects and developmental effects. MAA was postulated to be responsible for toxicity of EGME and other substances transformed to MAA.

Air concentrations of EGME between 8 ppm and 3960 ppm were measured in the conditions where anaemia, encephalopathy or neurological symptoms had occurred. (ECETOC, 2005 and the reference therein: Zavon, 1963; Greenburg *et al.,* 1938; Ohi and Wegman, 1978; Cohen, 1984; Cook *et al,* 1982; Denkhaus *et al,* 1986; Cullen *et al,* 1983; Shih *et al,* 2000a).

Several studies indicate that the EGME, EGEE or MEG exposures effected male reproduction or caused congenital malformations, mental retardation and chromosome aberrations in persons whose mothers had been occupationally exposed during pregnancy (ECETOC, 2005 and the reference therein: Sparer *et al.*1988; Welch and Cullen, 1988; Welch *et al.,* 1988; Saavedra *et al.,* 1997; El-Zein *et al* 2002).

11.2 Environmental effects assessment

Environmental risk assessment was not included in the ECETOC (2005) report.

Data on the environmental fate and the effects of MAA on the aquatic organisms are limited.

OECD study on the degradation potential of MAA indicated that MAA is readily biodegradable (study report, 1997), however another, non standard study indicated that MAA is not ready biodegradable (study report, 1984).

The following endpoints concerning aquatic organisms have been reported under REACH registration: short-term toxicity to fish *Brachydanio rerio,* 96 hour LC50: > 500 mg/L (study report, 1989), and 96-h acute toxicity study on *Leuciscus idus melanotus* LC50 was > 100 and < 215 mg (study report, 1988); aquatic invertabrates *Daphnia magna,* 48 hour EC50: 68.3 mg/L(study report, 1990); green algea *Desmodesmus subspicatus,* 72 hour ErC50: 66.2 mg/L (study report, 2010) and microorganisms EC50 on activated sludge > 1000 mg/L (study report, 1998); 16 hour EC50 for *Pseudomonas puitida* 96 mg/L (study report, 1990).

MAA was not considered as a subject for classification and labelling according to Directive 67/548/EEC and Regulation 1272/2008/EC by the REACH registrant.

The data publicly disseminated by ECHA have been summarized above, *for additional information on references see Confidential Annex.*

11.3 Derivation of DNELs

For the purpose of this analysis the authors of this dossier performed rough risk assessment utilizing information provided in the REACH registration, and previous reports by ECETOC (2005), WHO, (2009), ANNEX XV dossier for EGME (2010)[40]. MAA has been included by the ECETOC (2005) for assessment together with the group of glycol ethers. Using the extrapolation approach from the metabolic precursor of MAA, EGME and the toxicokinetics information, the NOAEL for MAA was calculated from NOAEL of EGME divided by factor of 2. DNELs for chronic, systemic effects of inhalatory exposure to MAA for workers and general population were derived.

The DNELs for workers and general population for inhalatory exposure as derived within work for this dossier, resulted in very low values $DNEL_{long\text{-}term\ inhalation}$values for workers (0.22 mg/m^3) or with the $DNEL_{long\text{-}term\ inhalation}$ values for the general population (0.056 mg/m^3). As a comparison a tolerable concentration of EGME was calculated to be 0.08 mg/m^3 by WHO (2009). This calculation was based on the NOAEC 32 mg/m^3 for developmental toxicity in experimental animals by inhalation (Hanley et al., 1984) and the default uncertainty factors for interspecies (10) and intraspecies (10) extrapolation and correction to continuous exposure (6/24 h).

Table 11 Derivation of DNELs

Type of value	Value / units	Explanation
NOAEC(EGME)	3 ppm	NOAEC of EGME developmental effects levels in inhalation study on rabbits (Hanley et al., 1984)
NOAEC(MAA)	1.5 ppm 5.6 mg/m^3	NOAEL based on studies on MAA was not established. The critical dose levels of MAA are expected to be lower than for EGME (ECETOC, 2005). The read across approach from the NOAEC(EGME) to NOAEC(MAA) was used, with the application of a factor of 2. 1 ppm (MAA) = 3.745 mg MAA/m^3 3 ppm / 2 = 3 x 3.745 (mg/m^3) / 2
Worker $_{corr}$NOAEC	0.75 ppm 2.8 mg/m^3	NOAEC corrected for different exposure conditions (REACH guidance Chapter R.8) $_{corr}NOAEC = {}_{inhal}NOAEC_{rabbit}$ x 6(h/day) / 8 (h/day) x 6.7 m^3 / 10 m^3
General population $_{corr}$NOAEC	0.37 ppm 1.4 mg/m^3	NOAEC corrected for 24 hours exposure (REACH guidance Chapter R.8) $_{corr}NOAEC = {}_{inhal}NOAEC_{rabbit}$ x 6(h/day) / 24(h/day)

[40] http://echa.europa.eu/documents/10162/b6b959c2-14c8-4612-9e91-cf181a867dd2

Worker $DNEL_{long\text{-}term,\ inhal,\ systemic\ effects,\ developmental\ effects}$	0.06 ppm 0.22 mg/m^3	The corrected NOAEC 2.8 mg/m^3 is used and assessment factors of 2.5 for interspecies (toxicodynamics) and 5 for intraspecies (workers)
Worker $DNEL_{long\text{-}term,\ systemic\ effects,\ developmental\ effects}$	0.032 mg/kg	Worker $DNEL_{long\text{-}term,\ systemic\ effects,\ developmental\ effects}$= Worker $DNEL_{long\text{-}term,\ inhal,\ systemic\ effects,\ developmental\ effects}$ (mg/ m^3) x Respiratory volume light activity for worker (wRV) 8h (m^3/person) / body weight (kg) = 0.22 x 10 / 70 = 0.032 mg/kg (REACH guidance Chapter R.8)
General population $DNEL_{long\text{-}term,\ inhalation,\ systemic}$	0.015 ppm 0.056 mg/m^3	The corrected NOAEC of 1.4 mg/m^3 is used and assessment factors of 2.5 for interspecies (toxicodynamics) and 10 for intraspecies (general population).
General population $DNEL_{long\text{-}term,\ systemic}$	0.016 mg/kg	General population $DNEL_{long\text{-}term,\ systemic\ effects,\ developmental\ effects}$= General population $DNEL_{long\text{-}term,\ inhal,\ systemic\ effects,\ developmental\ effects}$ (mg/m^3) x Respiratory volume for 24h (m^3/person) / body weight (kg) = 0.056 x 20 / 70 = 0.016 mg/kg (REACH guidance Chapter R.8)

11.4 Estimation of Risk characterisation ratios

Risk ratio for air freshener containing 0.5% MAA

$R_{airfreshener\ 0.5\%\ MAA}$ = Calculated MAA concentration in air / DNEL

1 $R_{airfreshener\ 0.5\%\ MAA\ /\ general\ population}$ = 0.0263[41] mg/m^3 / 0.056 mg/m^3 = 0.5

2 $R_{airfreshener\ 0.5\%\ MAA\ /\ general\ population}$ = 0.06[42] mg/m^3 / 0.056 mg/m^3 = 1

Conclusion: The exposure to MAA from airfreshener has been calculated with ConsExpo model. To evaluate a potential risk for consumers, a concentration equal to regulatory limit of 0.5 % MAA was assumed. The calculated daily mean concentration of MAA in the air was 0.0263 mg/m^3. This concentration was about 2 times lower than the maximum concentration provided in the air freshener product safety data sheet as calculated and provided by the producer (0.06 mg/m^3). Comparing those MAA calculated concentrations with the $DNEL_{long\text{-}term\ inhalation}$ values for the general population 0.056 mg/m^3 risk ratios were calculated to be in the range 0.5-1.

Considering the evidence indicating endocrine disrupting mechanism of MAA toxicity, and the uncertainty over the current standard risk assessment approaches reflecting those mechanisms, it is uncertain whether a risk ratio in the calculated range 0.5-1 really indicates low risk.

Risk ratio for home or professional use of cleaning products containing 0.3% MAA

[41] Value calculated in ConsExpo, see point 4.2.2.2

[42] Value estimated from information provided in SDS by the producer http://www.sca-tork.com/

$R_{cleaning\ products\ 0.3\%\ MAA}$ = Calculated MAA systemic exposure / DNEL

$R_{cleaning\ products\ 0.3\%\ MAA\ /\ worker}$ = 0.17 mg/kg bw/day / 0.032 mg/kg > **5**

$R_{cleaning\ products\ 0.3\%\ MAA\ /\ general\ population}$ = 0.17 mg/kg bw/day / 0.016 mg/kg > **10**

Conclusion: The exposure to MAA from hypothetical scenario of application of cleaning products has been calculated with ConsExpo model. In order to evaluate a potential risk for users (consumers or professional users), a theoretical concentration of 0.3% MAA was assumed The calculated MAA concentrations in air ranged from the maximum value of 1.2 mg/m^3 and the daily (8h) mean concentration 0.474 mg/m^3. Combined inhalatory and dermal exposure resulted in estimated internal exposure 0.17 mg/kg bw/day. Comparing this internal dose with the $DNEL_{long\text{-}term,systemic}$ for workers (0.032 mg/kg) and with the $DNEL_{long\text{-}term,\ systemic}$ for the general population (0.016 mg/kg) risk ratios were calculated. Results indicate that consumers and professional users could be at risk even if the concentration of MAA is within the regulatory limit of 0.3 % in such cleaning applications.

Risk ratio for professional use of cement cleaning product containing below 1% MAA

$R_{cement\ remover\ 1\%\ MAA}$ = Calculated MAA concentration in air / DNEL

$R_{cement\ remover\ 1\%\ MAA\ /\ worker}$ = 1.4 – 7 ppm / 0.06 ppm > **23**

Conclusion: The inhalatory exposure to MAA from application of cement cleaning product containing < 1% of MAA has been calculated with ECETOC TRA (version 3) model. Comparing MAA calculated concentrations with the $DNEL_{long\text{-}term\ inhalation}$ for workers (0.06 ppm) risk ratios were calculated. Dermal exposure can also occur but was not included in the exposure scenario. Results indicate that users could be at risk even if the concentration of MAA is within the regulatory limit in this type of application.