Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2,3-epoxypropyl methacrylate; glycidyl methacrylate

EC Number: 203-441-9
CAS Number: 106-91-2

CLH-O-0000001412-86-96/F

Adopted

4 December 2015

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

4 December 2015

CLH-O-0000001412-86-96/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: **2,3-epoxypropyl methacrylate; glycidyl methacrylate**

EC Number: **203-441-9**

CAS Number: **106-91-2**

The proposal was submitted by the **Netherlands** and received by RAC on **10 March 2015.**

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

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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 **5 May 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 June 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Elodie Pasquier**

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 4 December 2015** 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	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-123-00-4	2,3-epoxypropyl methacrylate; glycidyl methacrylate	203-441-9	106-91-2	Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* Eye Irrit. 2 Skin Irrit. 2 Skin Sens. 1	H302 H312 H332 H319 H315 H317	GHS07 Wng	H302 H312 H332 H319 H315 H317			D
Dossier submitters proposal	607-123-00-4	2,3-epoxypropyl methacrylate; glycidyl methacrylate	203-441-9	106-91-2	Carc. 1B Muta. 2 Repr. 1B STOT SE 1 Acute Tox. 4 Acute Tox. 3 Eye Dam. 1 Skin Corr. 1C Skin Sens. 1	H350 H341 H360F H370 (respiratory tract) (inhalation) H302 H311 H318 H314 H317	GHS08 GHS05 GHS06 Dgr	H350 H341 H360F H370 (respiratory tract) (inhalation) H302 H311 H314 H317			D
RAC opinion	607-123-00-4	2,3-epoxypropyl methacrylate; glycidyl methacrylate	203-441-9	106-91-2	Carc. 1B Muta. 2 Repr. 1B STOT SE 3 STOT RE 1 Acute Tox. 4 Acute Tox. 3 Eye Dam. 1 Skin Corr. 1C Skin Sens. 1	H350 H341 H360F H335 H372 (respiratory tract) (inhalation) H302 H311 H318 H314 H317	GHS08 GHS05 GHS06 Dgr	H350 H341 H360F H335 H372 (respiratory tract) (inhalation) H302 H311 H314 H317			D
Resulting Annex VI entry if agreed by COM	607-123-00-4	2,3-epoxypropyl methacrylate; glycidyl methacrylate	203-441-9	106-91-2	Carc. 1B Muta. 2 Repr. 1B Acute Tox. 4 Acute Tox. 3 STOT SE 3 STOT RE 1 Eye Dam. 1 Skin Corr. 1C Skin Sens. 1	H350 H341 H360F H302 H311 H335 H372 (respiratory tract) (inhalation) H318 H314 H317	GHS08 GHS05 GHS06 Dgr	H350 H341 H360F H302 H311 H335 H372 (respiratory tract) (inhalation) H314 H317			D

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The proposed classification of 2,3-epoxypropyl methacrylate or glycidyl methacrylate (GMA, used throughout this opinion) is partly based on glycidol, the *in vivo* metabolite of GMA. Its relevance for the hazardous properties of GMA is discussed below.

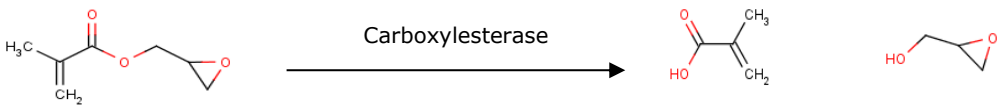
The toxicokinetic behaviour of GMA was investigated in rabbits. After an intravenous injection of 200 mg/kg bw, over 95% of the parent compound disappeared from the blood within 10 minutes. Following a subcutaneous injection at 800 mg/kg bw, the toxicokinetics appeared to fit with a one-compartment, open model with a first-order absorption. Subcutaneous co-administration of a carboxylesterase inhibitor resulted in about ten-fold higher maximum blood concentrations of GMA. The substance was metabolised in a first order process when incubated *in vitro* with whole blood, plasma, erythrocyte suspension and homogenates of various tissues (Shi Tao *et al.,* 1988).

In vitro incubations of ^{14}C-GMA with nasal epithelial tissue preparations and liver homogenates from human, rat and rabbit resulted in all cases in the formation of only one metabolite tentatively identified as glycidol (Domoradzki, 2004). At an initial concentration of 2 mM of GMA, the half-live of GMA (via hydrolysis) was shorter in incubations with rat and rabbit tissues as compared to human tissues (biotransformation of GMA in liver homogenates was completed within approximately 30 minutes versus 2 hours, respectively).

Although the metabolic transformation is expected to be slower in humans than in rodents, GMA is expected to transform completely into glycidol and methacrylic acid (MAA) in rodents as well as in humans.

No metabolite resulting from the action of epoxide hydrolase was identified *in vitro*. Epoxide hydrolase was hypothesised to produce glycerol methacrylate from GMA as an alternative pathway to the action of carboxylesterase. Epoxide hydrolase has been shown to be active in liver, kidney and lung tissues of 9 tested species including man and rodents (Pacifici, 1991). However, the absence of corresponding GMA metabolites after incubation with rat, rabbit or human liver tissues *in vitro*, provides evidence that the carboxylesterase pathway overrides the hypothetical epoxide hydrolase pathway for metabolism of GMA.

Figure 1: Proposed metabolism of GMA in mammals



GMA Methacrylic acid + glycidol

In addition, data were provided by the DS in order to compare the toxicological profile of GMA with glycidol and to support the use of glycidol data for the assessment of GMA. Relevant data for both GMA and glycidol are summarised in the table below.

Only data/studies considered as key with regard to reliability and their relevance for the comparison of GMA with glycid, are included in the table below.

Status/endpoint	Glycidol	GMA
Harmonised classification for local effects	Skin Irrit. 2 – H315 Eye Irrit. 2 – H319 STOT SE 3 – H335	Skin Corr. 1C – H314* STOT SE 3 – H335* *Agreed by RAC, resulting in the future Annex VI entry if adopted by COM.
Repeated dose toxicity – oral	90-day study – gavage –rats (Irwin *et al.*, 1990) ≥ 100 mg/kg bw/day: decrease in sperm count and motility ≥ 200 mg/kg bw/day: mortality 400 mg/kg: complete mortality by week 2. Cerebellum necrosis, demyelination in brain medulla, tubular degeneration and/or kidney necrosis, thymus lymphoid necrosis, testicular atrophy and/or degeneration 90-day study – gavage – mice (Irwin *et al.*, 1990) ≥ 19 mg/kg bw/day: decrease in sperm count and motility; testicular atrophy ≥ 150 mg/kg bw/day: mortality; decreased body weight; brain demyelination 300 mg/kg bw/day: complete mortality by week 2; renal tubular cell degeneration	45-day study – gavage – rats (MHWJ[1], 1997) ≥ 30 mg/kg bw/day: salivation and squamous hyperplasia and cell infiltration in the forestomach in males 100 mg/kg bw/day: increase in kidney and adrenal weights in males and cell infiltration in the forestomach of females. Decrease in fertility index assumed to be due to decreased sperm motility.
Repeated dose toxicity – inhalation	50-day study – rats (Hine *et al,* 1956) 1.2 mg/L (single dose): 1/10 death of bronchopneumonia. Very slight irritation of the eyes, with slight lacrimation and encrustation of the eyelids and slight respiratory distress following the first few exposures. No significant gross or microscopic lesions	14-day study – rats (Landry *et al.*, 1991) 0.06 mg/L: very slight multifocal necrosis of respiratory epithelium in the nasal cavity 0.23 mg/L: slight to moderate multifocal necrosis and inflammation of the respiratory and olfactory nasal epithelium 0.93 mg/L: animals sacrificed at day 4: severe necrosis and inflammation in the nasal cavity. General debilitation with noisy and difficult respiration, eye irritation, corneal clouding and distended abdomen ≥ 0.23 mg/L: decreased body weight 14-day study – rabbits (Cieszlak *et al.*, 1996) 0.012 mg/L: degeneration of the nasal olfactory epithelium (reversible) ≥ 0.029 mg/L: olfactory epithelial degeneration, hyperplasia, erosions, ulcers and inflammation of the nasal epithelium (not fully reversible) 90-day study –rats (Landry *et al.*, 1996) ≥ 0.09 mg/L: hyperplasia of respiratory epithelium of nasal cavity in all animals
Mutagenicity	Positive micronucleus assay in mice after two intraperitoneal (IP) injections: 3 times higher micronuclei incidence in high dose group (150 mg/kg bw) vs controls (Irwin *et al*,	Several positive assays *in vitro* Positive micronucleus assay in mice after a single gavage dose of 750/1000 mg/kg bw

[1] MHWJ: Ministry of Health and Welfare, Japan

	NTP, 1990) Harmonised classification Muta. 2 – H341	(MHWJ, 1997) Negative micronucleus assay in mice after single IP injection up to 300 mg/kg bw (Lick *et al.*, 1995)
Carcinogenicity	Induction of benign and malignant tumours in multiple organs in rats and mice of both sexes (Irwin *et al.*, NTP, 1990). Harmonised classification Carc. 1B; H350	No data
Reproductive toxicity	12-day study – oral – rats (Hahn, 1970) 15 mg/kg bw/day: infertility (reversible within 1 week) 90-day study – gavage – rats (Irwin *et al.*, 1990) ≥ 100 mg/kg bw/day: decrease in sperm count and motility 400 mg/kg bw/day: testicular atrophy and/or degeneration (general toxicity described above) 90-day study – gavage – mice (Irwin *et al.*, 1990) ≥ 19 mg/kg bw/day (lowest dose): decrease in sperm count and motility; testicular atrophy (general toxicity described above) Harmonised classification Repr. 1B – H360F	OECD TG 422 (45 days) – gavage – rats (MHWJ, 1997) 100 mg/kg bw/day: decrease in fertility index assumed to be due to decreased sperm motility

A comparison of the toxicological profiles shows that GMA is skin corrosive whereas glycidol is irritant to the skin. In addition, GMA induces local toxicity by the oral and inhalation route that is either not observed with glycidol or is observed at higher doses and with less severity than with glycidol. This finding is consistent with the hydrolysis of GMA to glycidol and methacrylic acid by carboxylesterase at the site of contact. Local transformation of GMA to methacrylic acid is expected to induce corrosive lesions, with a severity which is proportionate to the relative tissue and species-specific carboxylesterase activity.

Due to the difference in local toxicity, the maximum doses that can be administered to animals are lower for GMA than for glycidol. This may explain why the systemic effects that are observed at the highest doses after repeated exposure to glycidol by the oral route (severe effects on brain, kidney, thymus) are not observed with GMA. The effect of glycidol on male reproductive function appears to be a sensitive adverse effect of glycidol which is observed at the LOAEL in both rats and mice (Irwin *et al.*,1990). Comparable effects are reported with GMA in studies investigating fertility.

Similarly, both glycidol and GMA induce mutagenicity. *In vivo*, the effect was clearly identified at high doses (high considering the respective toxicity and route of administration used) for both compounds. In particular, the induction of micronuclei in erythrocytes of GMA via the oral route provided support to the assumption that glycidol is formed from GMA.

Taken together, similar effects of GMA and glycidol as evidenced by alteration of male fertility and genotoxicity support the conclusion that glycidol is formed in vivo from GMA, as also evidenced by the toxicokinetic data.

RAC notes that the toxicity of MAA has not been further discussed by the DS in the CLH dossier. However, on the basis of available in vitro and in vivo data, considering the extensive hydrolysis of GMA into glycidol and the consistency of several systemic effects, GMA is generally expected to produce similar systemic effects as glycidol. This applies in particular to the most sensitive systemic effects of glycidol whereas the the corrosivity of GMA may prevent the possibility to reach high systemic doses of glycidol as a result of GMA metabolism. Glycidol is only considered to be irritant to skin.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute toxicity - oral

Several acute oral studies were available, but all had limitations either in reporting or in the conduct of the study. A key study could therefore not be determined. The OECD has adopted (OECD, 1999) an oral LD_{50} value for GMA of 597 mg/kg bw in the rat, based on a study by Zdravko *et al.* (1985). Although the available studies were not reported in detail, all studies provided LD_{50} values within the same range (390 to 1050 mg/kg bw). Thus, the DS proposed to classify GMA for acute oral toxicity in category 4 (H302) as the LD_{50} values of all available studies were within the limits for classification in category 4 (300 - 2000 mg/kg bw).

Acute toxicity - inhalation

In an inhalation toxicity study performed according to OECD Test Guideline (TG) 403 (key study), there were no mortalities observed in rats exposed for 4 hours up to 2394 mg/m^3 GMA, the highest practically attainable vapour concentration. Laboured breathing and eye irritation were observed at the 2394 mg/m^3. Corneal opacity and decreased body weights were induced in all groups, even at the lowest concentration of 1563 mg/m^3 (Nitschke *et al.*, 1990).

In another inhalation toxicity study, acute exposure of rats with saturated vapour of GMA for 2 hours did not result in any deaths (Smyth *et al.*, 1969). It was reported that the saturated vapour concentration of GMA at 20°C was 474 ppm (2754 mg/m^3) (quoted in Workplace Environmental Exposure Level Guide 1999). Tests with higher concentrations of GMA, including aerosols were not performed. This study was considered as supportive because only very limited information was available. For example, information on mortalities at exposure durations longer than 2 hours was lacking.

Another study (Haag, 1953) reported that the lowest concentration that caused deaths was 1400 mg/m^3 for 6 h in rats, rabbits, guinea pigs and dogs. However, the study was not considered reliable by the DS.

Overall, no classification for acute inhalation toxicity was proposed by the DS, since the LC_0 in rats exposed for 4 hours was considered to be 2394 mg/m^3, the highest practically attainable vapour concentration. However, higher concentrations including aerosols were not tested and the DS concluded that no classification for acute inhalation toxicity was warranted for GMA, based on the absence of data.

Acute toxicity - dermal

The available information was very limited in the only available acute dermal toxicity study (Smyth *et al.*, 1969) and would normally not be usable for classification, according to the DS. However, GMA has an existing entry in Annex VI to the CLP with a minimum classification for acute dermal toxicity (category 4). It was considered likely by the DS that this study was the basis for the existing harmonised classification. Therefore, this study could be used according to the DS to adopt the existing minimum classification. The dermal LD_{50} for rabbits in this study was 480 mg/kg bw and the DS proposed to classify GMA for dermal acute toxicity in category 3 (H311).

Comments received during public consultation

One Member State (MS) requested clarifications on the reliability of some studies on acute toxicity by oral and dermal routes. Another MS raised doubts on whether the data were sufficiently reliable to remove the existing classification for acute inhalation toxicity.

Assessment and comparison with the classification criteria

Acute toxicity - oral

RAC agrees with the assessment made by the DS that all six results from the four available studies indicated acute oral toxicity within a similar range of doses and are altogether sufficient to conclude on the classification of GMA for acute oral toxicity. All available LD_{50} values in rats, mice and guinea pigs are within the range of 300 - 2000 mg/kg bw and a classification for **Acute Tox. 4; H302** is therefore warranted for GMA, according to CLP.

Acute toxicity - inhalation

A study performed according to OECD TG 403 (Nitschke *et al.*, 1990) reported no mortality in rats at the maximum achievable vapour concentration of 2394 mg/m^3 for 4 h. Two other studies were performed on vapours but both studies have limitations in their reporting (Smyth *et al.*, 1969) and/or in their reliability (Haag, 1953) and none of them provided a result that allows RAC to conclude on the LC_{50} value.

RAC concludes that none of the available studies, including a guideline study (Nitschke *et al.*, 1990), provides evidence of an LC_{50} value within the range of values for classification. **No classification for acute inhalation toxicity** is warranted.

Acute toxicity - dermal

An LD_{50} value of 480 mg/kg bw is available from an acute dermal toxicity study in rabbits which is within the range of 300 - 2000 mg/kg bw corresponding to a classification in category 3. Information on this study is very limited and its reliability cannot be assessed in detail by RAC. RAC notes however that the LD_{50} values obtained in the same publication (Smyth *et al.*, 1969) for acute oral toxicity are within a similar range of values as in other available oral studies providing some support to the reliability of the study. The LD_{50} obtained via the dermal route in rabbit is within a similar range as the LD_{50} values obtained via the oral route in rats, mice and guinea pigs. A higher LD_{50} is generally expected by the dermal route compared to the oral route but no information is available on the relative absorption of GMA by the different routes. Also, the studies of longer duration by oral route suggest that the rabbit is a more sensitive species to toxicity of GMA than the rat.

Considering these elements, RAC concludes that the LD_{50} of 480 mg/kg bw in rabbit by the dermal route is plausible. On this basis, RAC agrees with the DS proposal to classify GMA as **Acute Tox. 3; H311.**

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

Laboured breathing was induced in rats by acute inhalation exposure for 4 hours at 1563 mg/m^3 and 2394 mg/m^3 (Nitscke *et al.*, 1990). In another acute inhalation study, changes in e.g. lungs, thorax and respiration were observed in rats, rabbits, guinea pigs and dogs (Haag, 1953). In this study, exposure was conducted at 1400 mg/m^3 for 6 hours. No further details were available. The DS considered that these changes may have resulted from respiratory irritation of GMA.

According to the CLP criteria, the guidance values for placing a substance in category 1 after a single-dose exposure are ≤ 10 mg/L/4h for vapours (rat). Laboured breathing was found in the acute inhalation study at 1.563 mg/L/4h (Nitschke *et al.*, 1990) and thus the DS proposed to classify GMA as STOT SE 1 (damage to the respiratory tract after inhalation). According to the DS, this classification was also justified because severe multifocal necrosis and inflammation of the olfactory and respiratory nasal epithelium and congestion, inflammation and necrosis in the lung were observed in rats after 4 days (6-hours/day) of exposure to 0.931 mg/L of GMA (Landry *et al.*, 1991). Although the exposure was repeated for 4 days and the daily exposure period was

somewhat longer than 4 hours as referred to in the CLP Table 3.8.2 for single exposures, the exposure concentration was clearly below the guidance limit value of 10 mg/L for category 1. Therefore it was considered very likely that comparable respiratory tract irritation would have occurred also after a single exposure. According to the DS, it was probable that these effects had occurred in the available acute inhalation study, but that they were not observed due to the limited necropsy performed and the long post-exposure observation period in the acute study. Local respiratory tract tissue injury was also expected given the corrosive effect on skin and eyes.

The DS concluded that a classification with STOT SE 1 was required with the respiratory tract as a target organ and the inhalation route as the route of exposure.

Comments received during public consultation

Two MS noted that the CLP guidance does not recommend classification for STOT SE 1 or 2 if the effects are consequences of a corrosive mode of action and therefore did not support the proposed classification. One of them recommended a classification for STOT SE 3 (H335) instead, considering the respiratory effects observed in the acute inhalation studies. Both MS also proposed to consider classification for specific target organ toxicity after repeated exposure.

Assessment and comparison with the classification criteria

RAC considers that the effects observed on the respiratory tract after 4 days of a 6-hour daily exposure to 0.931 mg/l of GMA vapours demonstrate corrosivity of GMA vapours to the respiratory tract under these experimental conditions, which is consistent with the corrosive properties of GMA on skin and eyes (see section below). The severity of the effects (inflammation and necrosis) and the effect concentration (threshold value of 10 mg/L for category 1) are consistent with the criteria for STOT SE 1 but the effects were observed after a total of 24 h cumulated exposure. Thus, it is not possible to conclude that effects of similar severity would have occurred also after a single 4-hour exposure. However, the result supports the assumption that the clinical signs observed in the acute inhalation toxicity study can be attributable to respiratory tract irritation.

Significant functional changes, e.g. in the respiratory system, which are more than transient in nature, are considered to support classification as STOT SE 1 and 2. However, due to limited information, it is not possible to determine whether the clinical signs were transient or not.

RAC therefore considers that the data are not sufficiently robust to classify GMA for STOT SE in category 1 or 2.

However, laboured breathing and changes in the respiratory tract in the acute inhalation studies, in combination with the corrosive findings in the 4-day inhalation study and the skin corrosive properties, are considered by the RAC to be signs of at least transient respiratory tract irritation. Therefore, RAC supports classification of GMA as STOT SE 3; H335.

RAC is aware that the CLP guidance recommends that "an additional classification as specific target organ toxicant (single exposure, Category 1 or 2) is not indicated if the severe toxicological effect is the consequence of the local (i.e. corrosive) mode of action" while "the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier". However, RAC notes that the hazard statement H314 ("Causes severe skin burns and eye damage") does not include a reference to the respiratory tract. Thus, RAC recommends the additional classification of GMA as **STOT SE 3; H335**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

In an OECD TG 404 study (Lockwood, 1991), rabbits were examined 4, 24 and 48 h after a 4-hour exposure to 0.5 ml of GMA under occluve conditions. Oedema and/or erythema were observed at all time points in all rabbits. They were accompanied by moderate necrosis (score 4) in 2/6

animals at the last observation point of 48 h after exposure. When animals were exposed for 1 h, slight erythema and moderate erythema were observed in some animals. Necrosis was identified in 2 animals at 48 h and described as very slight in one (score 2) and superficial in the other (score 3). Reversibility or worsening of the lesions in this study could not be further assessed as no data was available later than 48 h after exposure.

Two other studies were considered by the DS as supportive despite their limitations. In a poorly reported study, a single covered topical application to the skin of an albino rabbit for 4 h induced moderate to severe skin irritation including necrosis with slight to moderate oedema and mortality (Olson, 1960). Necrosis was also reported after skin exposure to GMA under non-guideline conditions (0.1 ml, 5-day exposure) (Ou-Yang *et al.*, 1988).

The DS concluded that corrosive effects of GMA were observed in 2/6 rabbits after a 4-h exposure but not after 1 h (Lockwood, 1991). Thus, the DS proposed to classify GMA as Skin Corr. 1C.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

Necrosis was reported after a 4-h exposure to GMA both in the study by Lockwood (1991) and in the study by Olson (1960). In the former study, which was performed in accordance with OECD TG 404, necrosis was observed in 2/6 animals and was described as moderate 48 h after exposure. RAC considers that this result fulfils the criteria for classification as corrosive as the substance produces destruction of skin tissue in at least 1 tested animal after 4-h exposure. After a 1-h exposure, necrosis was observed in 2/6 animals and described as very slight to superficial 48 h after exposure. Although reversibility or worsening after 48 h is not known, RAC considers that superficial necrosis does not fulfill the definition of destruction of skin tissue and that the criteria for classification in subcategory 1B are not met.

RAC therefore concludes that GMA should be classified as **Skin Corr. 1C; H314**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

There was only one eye irritation study available (Olson, 1960) which had some resemblance to the OECD TG on eye irritation but the study was limitedly reported. Furthermore, the effects were differently described in the study report available to the DS, REACH registration dossier and OECD SIDS summary (1999). In the unwashed eye, undiluted GMA induced slight to moderate conjunctivitis. Slight corneal injury that cleared within one week was described in the study report while corneal damage that did not heal within 7 days was reported in the OECD SIDS summary (1999) and REACH registration dossier. Therefore, the DS considered that the results were not reliable although they indicated that GMA had the potential to induce eye irritation.

Two supporting studies performed using inhalation exposure, reported corneal opacity from 610 mg/m^3. In the acute toxicity study (Nitschke *et al.*, 1990), this effect did not heal within 14 days post-exposure. Despite that this indicated a clear irritating effects on the eye, this was considered by the DS to be due to exposure to the vapour and not to the liquid.

Comments received during public consultation

One MS noted that the hazard statement H318 shall not be included in the labelling to avoid redundancy with H314.

Assessment and comparison with the classification criteria

Section 3.3.2.4 in the Guidance on the application of the CLP criteria (version 4.1) states that "A skin corrosive substance is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage). Thus, in this case both classifications (Skin Corr. 1 and Eye Dam. 1) are required but the hazard statement H318 'Causes serious eye damage' is not indicated on the label because of redundancy (CLP Article 27)."

RAC concluded that GMA should be classified as **Skin Corr. 1C; H314.** Classification as **Eye Dam. 1** should also be added, but **without labelling with hazard statement H318**.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

Respiratory sensitisation was not reported in any of the acute and sub-acute inhalation studies. However, these tests were not developed to determine the respiratory sensitising potential of substances. No classification for respiratory sensitisation was warranted because of the absence of data.

Comments received during public consultation

One MS noted that asthma is a common finding associated with exposure to methacrylates and made a request for potential human cases related to GMA exposure. The DS had not identified any such human cases.

Assessment and comparison with the classification criteria

The association of exposure to methacrylates, in particular to methyl methacrylate (Savonius, 1993, Borak, 2011), with cases of asthma raises a concern that GMA has a potential for respiratory sensitisation. However, in the absence of animal or human data showing respiratory sensitisation of GMA, and since data necessary in order to get a clear understanding of the sensitising and/or irritant properties of members within the group of methacrylate are currently not available to the RAC, RAC recommends **not to classify GMA for respiratory sensitisation**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Several animal studies and human data as presented by the DS in the CLH report, are summarised in the tables below.

Table: Summary of animal data

Test	Induction	Challenge	Results	Klimisch score	Limitation	Reference
Buehler test	25% reduced to 10% at 3rd application in DPGME*	1%	7/10 positive (slight erythema)	2 (reliable with restrictions)	No control group	Dow 1990
Test on guinea pigs	No data	No data	6/6 positive	4 (not assignable)	Very limited information	BIBRA 1988
Delayed allergic	0.1 ml of 1% GMA in acetone for 10 days – skin	No data	7/10 positive (hyperaemia, oedema,	4 (not assignable)	Limited information	Ou-Yang *et al.,* 1988

reaction test	smear		scleroma, necrosis)			
Delayed allergic reaction test	0.1 ml of 1% GMA in acetone for 10 days – intradermal injection	No data	6/10 positive (hyperaemia, oedema, scleroma, necrosis)	4 (not assignable)	Limited information	Ou-Yang *et al.,* 1988
Rapid allergic reaction test (active stimulation)	0.5% GMA with homologus serum albumin – intradermal injection	0.5% GMA with homologus serum albumin – intravenous	5/5 positive (breathing difficulties, wheezing, increased mouth and nose secretions, spasms, death)	4 (not assignable)	Limited information	Ou-Yang *et al.,* 1988
Rapid allergic reaction test (passive stimulation)	Diluted serum from sensitised animal injected subcutaneously 1 h before challenge	0.5 ml of 0.1% GMA with homologus serum albumin – intravenous	5/5 positive (blue circles or spots)	4 (not assignable)	Limited information	Ou-Yang *et al.,* 1988

* Dipropylene glycol monomethyl ether

Table: Summary of human data

Test	Subjects	Conditions	Results	Klimisch score	Reference
Human patch test	3 cases of allergic contact hypersensitivity to GMA used in adhesive sealant manufacturing	Closed and open patch test with 1% GMA in petrolatum	3/3 positive (erythema, oedema, vesiculation)	2 (reliable with restrictions)	Dempsey, 1982
Human patch test	A 31-year-old non-atopic woman, who had worked in contact with acrylate derivatives including GMA	0.01% and 0.05% in acetone	Positive to GMA and ethoxyethyl acrylate in the European (meth)acrylate series	2 (reliable with restrictions)	Matura, 1995

The key study (Dow, 1990) showed erythema in 7 out of 10 guinea pigs dermally induced with 25% GMA (reduced to 10% for the third induction) and dermally challenged with 1% GMA. The study resembled the Buehler test, but was lacking a negative control group. The induction dose of 10% induced some local effects. However, according to the DS, the significant reduction in the challenge dose suggested that the observed effects were the result of sensitisation and not irritation. The results of the key study was supported by other tests which were reported with limited details or were conducted using a different, non-standard, approach. Although the predictive value of these types of studies was considered to be largely unknown, the results were considered positive. There were also a limited number of human cases reported.

Based on the available studies, the DS proposed to classify GMA for Skin Sens. 1: H317.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

70% of positive reactions were obtained in the key Buehler study (Dow, 1990), which did not include a negative control group. GMA is corrosive for skin and produced slight erythema in some animals after the second induction application with a concentration of 25%. The third induction dose was reduced to 10%. The reaction to the 1% challenge dose was slight erythema. Since the challenge concentration is considered sufficiently lower than 25%, irritant effects are unlikely and positive reactions are expected to be the result of sensitisation. The incidence of 70% of positive reactions exceeds the minimum level of 15% of responding animals according to the classification criteria for sub-category 1B in case the induction dose is above 20%. However, the induction concentration was changed from 25% to 10% GMA during the assay and it is therefore not possible to establish whether an incidence of 60% of positive reactions would have been obtained at a topical induction dose between 0.2% and 20% which would lead to classification in sub-category 1A according to the criteria for classification. No sub-categorisation is therefore proposed by RAC for GMA.

RAC notes that the results from other animal studies were of limited reliability due to the absence of detailed information and the use of non-standard protocols. However, all showed positive reactions. In addition, although positive for skin sensitisation, the human data addressed a very small number of cases. Altogether, RAC is of the opinion that these additional studies support the conclusion that GMA is a skin sensitiser.

RAC agrees with the DS that, taken together, the data support the existing classification of GMA as **Skin Sens. 1; H317**.

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

Summary of the Dossier Submitter's proposal

According to the DS, the effects observed after repeated oral and dermal exposure were limited to local effects and were caused by the irritating/corrosive properties of GMA. The DS considered it probable that these effects were concentration-dependent and would occur already after a single exposure at concentrations not so different from the dose levels at which these effects were actually observed in the repeated dose study. However, such effects were considered more relevant for consideration of an acute toxicity classification. Therefore, based on the available studies and the other classifications proposed by the DS, i.e. STOT SE 1 (with the respiratory tract as a target organ and the inhalation route as the route of exposure) and Acute Tox. 3 and 4 for the dermal and oral route, respectively, no classification of GMA for this hazard class was proposed by the DS.

Comments received during public consultation

Two MS proposed a classification for STOT RE 1 for the inhalation route, on the basis of local effects observed in the respiratory tract at concentrations lower than in acute inhalation exposure studies. One of them also pointed out the systemic effects observed in the 26-week inhalation studies (Ouyang Guoshun *et al.*, 1990).

Assessment and comparison with the classification criteria

By the oral route, severe toxicity including 20% deaths was described in rabbits after 15 days of exposure to 50 mg/kg bw/day (Ou-Yang *et al.*, 1988). The reporting of the study was limited, the purity of the test substance was low (92%) and the effects were not consistent with the effects observed in the acute toxicity studies, in which the LD_{50} values ranged from 390 to 1050 mg/kg bw in rats, mice and guinea pigs. The result was also not consistent with the results in the combined repated dose and reproductive toxicity screening study (MHWJ, 1997) in which severe effects were restricted to the gastrointestinal tract of rats exposed to 100 mg/kg bw/day for 45 days. It is therefore uncertain whether the severe effects in rabbits should be attributed to higher

sensitivity of rabbits as compared to rats and/or to other potential factors such as toxicity of impurities. The combined study (MHWJ, 1997) is considered to be the only study sufficiently reliable upon which a discussion on classification for repeated dose toxicity via the oral route can be based upon. At doses relevant for classification for STOT RE 2, salivation, forestomach hyperplasia and cell infiltration were observed. Considering the corrosivity of the test substance, these finding are considered adaptative to repeated irritation, in particular in relation to administration by gavage. RAC therefore agrees with the DS that GMA does not warrant classification for repeated toxicity via the oral route.

By inhalation, systemic toxicity in several target organs was observed only in the 26-week study in rats and rabbits. No systemic effects were reported in other available studies, in particular at the high dose of the 13-week study which was 6 times higher than the low dose in the 26-week study. Considering also the uncertainties raised by the study author on the purity of the test substance, this study was not considered to form a reliable basis for classification.

Local effects in the upper respiratory tract were observed in all 2-week and 13-week studies. At doses relevant for classification for STOT RE 1, multifocal necrosis and inflammation of the nasal epithelium were observed after 2 weeks of exposure in rats and rabbits. Necrosis was slight to moderate in rats at 0.23 mg/L and erosions, ulcers and changes, partially reversible after 4 weeks of recovery, were reported in rabbits from 0.012 mg/L. Hyperplasia of the respiratory epithelium was observed in rats at 0.09 mg/L in the 13-day study. These effects are consistent with the corrosive effects of GMA. The corrosive effects of GMA on the respiratory tract are the basis for the agreed classification for STOT SE 3 for respiratory irritation (see section above). However, RAC considers that significant local effects occurred in repeated dose toxicity studies at doses lower than the effective doses after acute exposure: effective doses of 1.4 to 2.4 mg/L were reported after a single exposure and of 0.9 mg/L after a 4-day exposure whereas the effective doses after repeated exposure were 0.23 and 0.029 mg/L in the two-week studies in rats and rabbits, respectively.

According to the Guidance on the Application of the CLP criteria (version 4.1) (section 3.9.2.5.1) repeated dose effects which occur at doses more than half an order of magnitude lower than the dose that mediates the evident acute toxicity effects (in this case, corrosivity) could be considered to be a repeated dose effect distinct from the acute toxicity. On this basis, RAC concludes that classification of GMA as **STOT RE 1 (respiratory tract) (inhalation)** is justified.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Genotoxicity studies on GMA *in vitro* showed positive results. In a micronucleus tests *in vivo*, oral administration of GMA increased the frequency of micronucleated polychromatic erythrocytes at the highest dose only. Other *in vivo* genotoxicity studies were mostly negative, including micronucleus tests with intraperitoneal (IP) administration and a gene mutation study with transgenic Big Blue Fischer 344 rats. The negative IP micronucleus test by Lick *et al.* (1995) was performed at lower exposure levels compared to the positive oral micronucleus study. According to the DS the choice of a lower dose in the IP studies could be explained by a higher mortality after IP exposure to the unprotected peritoneal compartment as compared to the stomach after oral exposure. Similar dose levels as applied in the IP studies did not induce positive responses either in the oral study. Also no decrease in PCE% was observed in the IP study at the highest dose level in contrast to what was observed at the highest dose level in the oral study.

Furthermore, *in vitro* and *in vivo* studies indicated carboxylesterase-mediated hydrolysis of GMA to glycidol. Glycidol, a metabolite of GMA, is already classified for Muta. 2 under CLP. Based on the available studies with GMA itself and on evidence on glycidol, GMA was considered by the DS to be mutagenic in somatic cells. There was only one *in vivo* study on germ cells of mice which showed a significant increase in unscheduled DNA synthesis (UDS) in male germ cells. However, the increase was small and not dose related. The DS concluded that GMA should be classified as Muta. 2; H341.

Comments received during public consultation

Classification as Muta. 2; H341 was supported by one MS. Another MS suggested Muta. 1B; H340 based on the sperm abnormalities observed in one study.

Assessment and comparison with the classification criteria

No human data are were available and classifications as Muta. 1A is not warranted.

> *"The classification in Category 1B is based on:*
> *– positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or*
> *– positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or*
> *– positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people".*

One study (Xie *et al.*, 1990b) provided some evidence of genotoxicity in germ cells *in vivo*. The observed unscheduled DNA synthesis (UDS) was slight (24-25% above controls) but the effect induced by the positive control was also slight (+29%). The reliability of this study was, however, uncertain and the result was obtained via the IP route. Infertility observed in males at 100 mg/kg bw/day via the oral route (MHWJ, 1997) may also indicate that GMA is able to reach the germ cells and to induce mutagenity. However, the mode of action has not been investigated and there is no direct evidence that GMA is bioavailable to germ cells and can induce mutagenicity in germ cells via a physiological route of exposure. The data are therefore considered insufficient to warrant classification as Muta. 1B.

> *"The classification in Category 2 is based on:*
> *– Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:*
> *– Somatic cell mutagenicity tests in vivo, in mammals; or*
> *– Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays."*

GMA induced micronuclei in mouse erythrocytes in an OECD TG study (MHWJ, 1997) providing evidence of somatic cell mutagenicity *in vivo* meeting the classification criteria for Muta. 2. In contrast, negative results were obtained in an IP study of good quality (Lick *et al.*, 1995). However, it is noted that positive results were obtained at the high dose (750/1000 mg/kg bw) via the oral route whereas the highest dose tested by the IP route was only 300 mg/kg bw. Comparison of the bioavailablility of the test substance/metabolite(s) in the target cells after dosing via two different routes of exposure is usually not directly possible in the absence of information on the relative absorption via the two routes. However, it is noted that the LD_{50} values obtained via the IP route (290-350 mg/kg bw) do not differ very substantially from LD_{50} values obtained via the oral route (390-1050 mg/kg bw). The discrepancy between the results on mutagenicity obtained via the oral and IP routes remains overall unclear, but RAC concludes that the negative result via the IP route cannot invalidate the clear mutagenic response observed via oral route at the high dose. The mutagenic potential of GMA is also supported by a consistent induction of genotoxic effects in the numerous *in vitro* studies that are available.

In addition, GMA is metabolised into glycidol (and methacrylic acid). Glycidol induces micronuclei and has an existing entry in Annex VI to the CLP Regulation as Muta. 2; H341. Glycidol also induces tumours in multiple tissues, which is consistent with a mutagenic mode of action. Glycidol data are considered as supportive evidence of GMA mutagenicity.

Considering these data, RAC concludes that a classification of GMA as **Muta. 2; H341** is warranted.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

There were reports on chronic exposure studies with GMA, but each one had significant methodological deficiencies; thus the DS concluded that there were no acceptable chronic studies with GMA.

In a very limited one-year study (Hadidian *et al.*, 1968), rats (3 males and 3 females) were dosed 5 days/week by gavage at 0.1 mg/kg bw/day. Groups of 15 male and 15 female rats were also dosed at 0.3 mg/kg bw/day. The authors concluded that no tissue effects related to the treatment were found. However the doses applied were considered too low. There was also a 26-week inhalation toxicity study at concentrations of 15.3 and 206 mg/m^3 in rats and rabbits (Ouyang Guoshun *et al.*, 1990). A wide range of toxic effects were observed in both species at both concentrations. However, because of the low purity of the material used (92%), the authors of the study suggested that the effects may have been caused by the impurities present. Therefore the DS considered it questionable whether the systemic toxicity was caused by GMA.

Consequently, a read across approach was used by the DS for GMA: although the kinetics of carboxylesterase-mediated hydrolysis of GMA appeared to be species-dependent, the primary metabolite of GMA in humans, rats and rabbits was glycidol. Chronic bioassay data were located for glycidol in rats and mice, which were clearly positive and glycidol is classified as Carc. 1B according to Annex VI, CLP. Thus, the read-across approach was based on the formation of a metabolite of GMA which is a known carcinogen (Carc. 1B).

Based on the available studies on glycidol, the DS proposed to classify GMA as Carc.1B; H350.

Comments received during public consultation

Two MS were in support of the proposed classification as Carc. 1B.

Assessment and comparison with the classification criteria

RAC concludes that the chronic data available on GMA present methodological limitations (low number of animals, limited purity) and were not performed at sufficiently high doses or for sufficient duration to provide a reliable information on the carcinogenic potential of GMA. The assessment of the carcinogenic potential of GMA is therefore based on data available for the metabolite glycidol.

Glycidol induced benign and malignant tumours in multiple organs in rats and mice of both sexes (Irwin *et al.*, 1990). It is noted that the increase in several tumours was observed from the lowest dose of 37.5 mg/kg bw/day. Glycidol has an existing entry in Annex VI to the CLP Regulation with a classification as Carc. 1B; H350.

Toxicokinetic data show that GMA is extensively metabolised into glycidol (and methacrylic acid) which is further supported by the consistency between the systemic toxicity profile of GMA and glycidol. RAC notes that although a more comprehensive analysis of other substances metabolised into glycidol (or to similar metabolites) would have provided additional support, GMA is expected to produce similar systemic effects as glycidol, on the basis of the available data. Local toxicity is different between GMA and glycidol and the corrosivity of GMA may prevent a high exposure to glycidol arising from metabolism of GMA. However, the data on male fertility supports the conclusion that the most sensitive systemic effects of glycidol can be observed after oral exposure to GMA in the absence of severe local toxicity. In addition, the induction of tumours at multiple sites in both males and females in two rodent species is consistent with the identification of glycidol as a genotoxic, non-threshold carcinogen and GMA is also identified as genotoxic *in vivo*.

Altogether, RAC concludes that classification as **Carc. 1B; H350** is warranted for GMA.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

An oral toxicity study was performed on GMA in CD (Crj: CD) rats according to OECD TG 422 (a combined repeated dose and reproductive/developmental toxicity screening test). Administration was conducted by gavage at doses of 10, 30 and 100 mg/kg bw/day from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. The fertility index (number of pregnant animals/ number of sucessfully mated animals) decreased significantly at 100 mg/kg bw/day.

Male mice injected IP with 5 consecutive daily doses of 0, 25, 50 or 100 mg/kg bw/day of GMA showed an increase in the percentage of abnormal sperm and decrease in the number of sperm. These results were confirmed in a subsequent study where mice were dosed IP with 0, 5, 25 or 100 mg/kg bw/day for five consecutive days. At 100 mg/kg bw/day, mice had decreased caudal epididymal weights, slightly lower testicular weights, decreased sperm counts and increased abnormal sperm. Mice given 25 mg/kg bw/day showed decreased sperm counts and increased abnormal sperm. These results might support the decreased fertility index of the rat study at 100 mg/kg bw/day, according to the DS.

In addition, the DS noted that glycidol, a metabolite of GMA, has an existing entry in Annex VI to the CLP Regulation with a classification as reproductive toxicant category 1B for adverse effects on sexual function and fertility (Repr. 1B; H360F).

Three reliable developmental studies via two different routes of exposure, oral and inhalation, indicated no teratogenicity even at the highest doses which showed maternal toxicity. The significant increase in foetal resorptions was considered as a basis for classification for developmental toxicity. However, as this effect was not observed in the comparable OECD TG 422 study (same route and dose levels), was only observed in the presence of maternal toxicity and since the main metabolite glycidol is not classified for development (Annex VI, CLP), no classification was proposed by the DS.

Based on the available studies on GMA and on data for glycidol, the DS proposed to classify GMA in category 1B for adverse effects on sexual function and fertility (Repr. 1B; H360F).

Comments received during public consultation

Two MS were in support of the proposed classification Repr. 1B for adverse effects on sexual function and fertility.

Assessment and comparison with the classification criteria

Fertility

No human data are available and classification Repr. 1A is therefore not appropriate.

Clear evidence of an impaired fertility is available in rats via oral route from a guideline study (MHWJ, 1999). The effect occurred at the highest dose of 100 mg/kg bw/day. At this dose, effects on adrenal and kidney weight without histopathological changes as well as local toxicity in the gastrointestinal tract (squamous cell hyperplasia and cell infiltration in the forestomach) were observed. However, RAC considers that the clear effect on fertility cannot be a secondary non-specific consequence of the other toxic effects, that were mainly local effects.

Additional studies via the IP route provide evidence that the fertility in males is affected. Investigations of sperm parameters and reproductive organs have identified an effect on sperm count as well as on sperm morphology. RAC notes that genotoxicity was also reported in male germ cells after IP injections (Xie *et al.*, 1990b). An effect on sperm motility without further details, was also reported in infertile rats exposed to GMA via the oral route (MHWJ, 1999).

Toxicokinetic data shows that GMA is extensively metabolised into glycidol (and methacrylic acid). RAC notes that although a more comprehensive analysis of other substances metabolised into glycidol (or to similar metabolites), would have provided additional support, GMA is expected to produce similar systemic effects as glycidol, on the basis of the available data. Studies

investigating fertility showed that glycidol induced male infertility. Although effects on sperm parameters were not affected in several studies, a decrease in sperm count and motility was identified in rats and mice in one study with glycidol (Irwin *et al.*, 1990). These data are consistent with the results of studies with GMA. It supports the conclusion that GMA can induce male infertility and that the effect is not secondary to the local toxicity of GMA, in particular since local toxicity is not observed with glycidol.

Although data point toward a direct action on sperm cells, there is overall no clear understanding on the mode of action of the effects of glycidol and GMA on male fertility and none of the available information raises questions concerning the relevance of the effects to humans.

In conclusion, RAC agrees with the DS that GMA meets the classification criteria as **Repr. 1B; H360F**.

Developmental toxicity

Developmental toxicity was not observed in two inhalation rabbit studies or in one oral (gavage) OECD TG 422 rat study (MHWJ, 1997) A significant increase in fetal resorptions at the highest dose of 108 mg/kg bw/day was observed in a second oral (gavage) rat study (Ou Yang *et al.*, 1988). Such an effect was not observed in the OECD TG 422 guideline rat study at the same dose (MHWJ, 1997). However, only two dams were pregnant at this dose in the MHWJ (1997) study. Thus, based solely on this study, it is not possible to draw a sound conclusion on the possibility of GMS to induce fetal resorptions at 100 mg/kg bw/day. No effects were observed at lower doses in any of the studies available.

RAC notes that the study by Ou Yang *et al.* (1988) was performed on GMA of low purity and it cannot be excluded that some impurities may have played a role in the induction of fetal resorptions at the highest dose. Thus, the reliability of this result is uncertain.

RAC concludes that **no classification is justified for developmental effects** based on the lack of reliable data, in particular the data from the highest doses via the oral route.

Additional references

Borak J., Fields C., Andrew L.S. and Pemberton M.A. Methyl methacrylate and respiratory sensitisation: a critical review. *Critical Reviews in Toxicology*, 2011; 41(3): 230-268.

Savonius B., Keskinen H., Tuppurainen M., Kanerva L. Occupational respiratory disease caused by acrylates. *Clinical and Experimental Allergy*, 1993; 23(5): 416-424.

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).