Commentaar op conceptadvies Ethyleenglycol

Comments on draft report Ethylene glycol

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Dit document bevat de letterlijke weergave van de commentaren (deels Engelstalig) van:

1 Delrin Netherlands
2 Cefic sector group

This document contains the comments (partly in Dutch) by:

1 Delrin Netherlands
2 Cefic sector group

Van:	Rosman, Roelant
Aan:	GR_draftOSH
Cc:	KUPPEVELT, Michiel van (VNCI)
Onderwerp:	Ethyleenglycol (Ethaan- (1,2-)diol) – casnr. –107-21-1
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Geachte heer Dr. R.H. Mennen,

Gedurende de commentaarperiode heb ik het conceptrapport gelezen via de website van de Gezondheidsraad.

Graag zou ik wille weten wat de effecten zijn bij inhalatie en dermale blootstelling.

Dit zijn blootstellingroutes bij gebruik van blusschuim bij ons en als spray bij maintenance.

Indien deze routes niet zijn onderzocht dan stel ik voor niet te classificeren voor effecten op de vruchtbaarheid, vanwege inconsistente en onvoldoende gegevens.

Met vriendelijke groeten,

Roelant Rosman

EHS Manager
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Name: Stany Serrien

Title: Cefic Sector Group Manager

Organization: Ethylene Oxide Ethylene Glycol, a Cefic sector group.

Subject: Public Consultation Comments on the Draft Advisory Report for Ethylene Glycol: Proposal to oppose against the proposed classification as developmental toxicant cat. 1B.

Dear Members of the Subcommittee,

We appreciate the opportunity to submit our formal scientific comments regarding the public draft advisory report for ethylene glycol (EG), issued on 16 March 2026. This response focuses specifically on Chapter 7 "Adverse effects on development", and the committee's subsequent recommendation to classify ethylene glycol as a Category 1B Developmental Toxicant (H360D).

While we acknowledge the committee's meticulous review of the available literature on test animals, in our view, the criteria for classification as a Category 1B developmental toxicant are not met.

The proposed classification appears to rely primarily on rodent data, which does not provide a suitable basis for human hazard identification in this case. Under the criteria set forth by the EU CLP Regulation (EC) No 1272/2008, a weight-of-evidence evaluation of the underlying comparative toxicokinetics clearly demonstrates that the rodent model is an artificial outlier for human prenatal risk regarding this specific metabolic pathway. Conversely, the rabbit model which shows no developmental toxicity, aligns closely with human physiology and therefore represents the more appropriate surrogate for assessing human prenatal development.

The overall body of evidence supports this conclusion across three key considerations:

1. Species-specific placentation & transporter biology: the human-rabbit synergy
2. High-dose metabolic overload & saturation of kinetic pathways
3. Route-of-exposure weight of evidence and confounding artifacts

1. Species-specific placentation & transporter biology: the human-rabbit synergy

The draft report correctly highlights that while oral administration of ethylene glycol induces serious, irreversible skeletal and visceral malformations, post-implantation

loss, and lower fetal body weights in rats and mice, no developmental toxicity or teratogenicity is observed in rabbits up to dose levels causing severe maternal systemic toxicity.

The committee also correctly notes that this striking species divergence is driven by differences in the accumulation of glycolic acid (GA), the primary toxic metabolite responsible for developmental toxicity. Crucially, the committee acknowledges that "there is suggestive information on similarities between humans and rabbits related to yolk sac physiology and MCT orientation", yet concludes that this is not sufficiently convincing to exclude the rodent data.

We challenge this dismissal. In early embryonic development, coinciding with the critical window of susceptibility for structural malformations, the directional orientation and expression of Monocarboxylate Transporter 1 (MCT1) in the maternally-facing epithelium of the yolk sac differs fundamentally across species:

a) Rodent physiology (susceptible): In rats and mice, early MCT1 expression functions as an active concentrator of monocarboxylates. When maternal clearance pathways are overwhelmed, this transporter rapidly pumps GA across the yolk sac, establishing a fetal *Cmax* inside the rat embryo reaching 150% of the maternal blood concentration [1-3]. To provide additional evidence, the Cefic Ethylene Oxide/Ethylene Glycol Sector Group is presently carrying out an *in silico* molecular docking study evaluating the interaction of glycolic acid with MCT1 and MCT4 in both human and rat. The study is expected to be completed within the next few months and will be made available thereafter. So far preliminary results have shown there is no binding of GA to human MCT 4.

b) Rabbit and human physiology (insensitive/protected): In rabbits and humans, embryonic yolk sac placentation and the anatomical orientation of MCT1 mirror each other. This inverted biological barrier drastically restricts or delays the entry of GA into the embryo. Consequently, Carney et al. (2008) demonstrated that the maximum concentration of GA in the rabbit embryo reaches only 30% of the maternal blood concentration [1-2]. Furthermore, even when a high dose of 1000 mg/kg bw/day EG is administered, the peak GA concentration (*Cmax*) in rabbit maternal blood reaches less than half (46%) of the corresponding levels in rats.

Under CLP Annex I, Section 3.7.2.2.1, animal data may be used to discount or down-categorise classification if there is clear evidence that the toxicological mechanism is not relevant to humans. The close anatomical and functional alignment of human and rabbit early yolk sac barriers demonstrates that human embryos will not experience the rapid, high intra-embryonic influx of GA necessary to trigger structural malformations. Therefore, the negative rabbit data is the true reflection of human hazard.

2. High-dose metabolic overload & saturation of kinetic pathways

A rigorous assessment under CLP criteria requires an integrated evaluation of the dosages at which reproductive effects occur. According to established standard international testing practices (e.g., OECD Test Guidelines), a limit dose of 1000 mg/kg bw/day is mandated for screening developmental hazards in test animals [4].

As documented in the advisory report, the overwhelming majority of the teratogenic findings in rodents occurred strictly at extreme bolus gavage doses exceeding the threshold of 1000 mg/kg bw/day:

1) Price et al. (1988) utilised oral gavage doses of 1250 and 2250 mg/kg bw/day in CD rats [5].
2) Carney et al. (1999) utilised a single massive gavage dose of 2500 mg/kg bw on gestation day 10 in Sprague-Dawley rats [6].
3) Neeper-Bradley et al. (1995) observed skeletal malformations in CD-1 mice predominantly at 1500 mg/kg bw/day [7].

At these extremely high, physiologically irrelevant clinical dose levels, the maternal metabolic enzyme systems (alcohol and aldehyde dehydrogenases) become completely saturated [8-10]. This kinetic saturation induces a non-linear, exponential spike in maternal plasma GA concentrations and severe maternal metabolic acidosis. In human occupational settings, exposure would not be bolus-type and low-dose (or concentration), meaning metabolic clearance remains fully operational, and maternal or fetal accumulation of GA to these toxic thresholds is biochemically impossible.

ECHA and CLP guidance explicitly indicate that when developmental toxic effects occur at dose levels that cause severe systemic distortions or exceed the standard limit dose guideline, a Category 1B classification may not be appropriate [11-12]. In the case of EG, the rodent malformations are an artifact of high-dose metabolic overloading rather than a manifestation of an intrinsic developmental hazard.

3. Route-of-exposure weight of evidence and confounding artifacts

Potential occupational/consumer exposure to ethylene glycol predominantly occurs via dermal contact or inhalation of mists or vapours during usage (such as window de-icing). In the draft report it is correctly noted that "studies with inhalation or dermal exposure routes in rats and mice showed no or equivocal developmental effects" compared to artificial oral gavage bolus studies. The committee tentatively attributes this to "limited uptake" without further specification or argumentation.

However, the underlying data from these non-oral studies reveal critical confounding variables that weaken the rationale for cat. 1B classification in addition:

1) In the whole-body inhalation studies conducted by Tyl et al. (1995) [13], wet fur was observed on all EG-exposed rodents. Subsequent quantification of ethylene glycol on the fur proved that oral ingestion via grooming was actually the primary driver of exposure, accounting for 64% to 90% of the internal dose.
2) When true non-oral routes are isolated to prevent oral grooming artifacts—such as compliant dermal exposure studies or nose-only inhalation designs—ethylene glycol failed to demonstrate teratogenic properties, as only minor variations rather than structural malformations were noted.

In addition, the "clear evidence of an adverse effect" required for Category 1B classification is missing when the adverse effects were only observed above limit dose (i.e. 1000 mg/kg bw/day).

Conclusion and recommendation for re-classification

In summary, the biological data for ethylene glycol indicates that its developmental toxicity is a highly restricted, non-linear phenomenon specific to rodents. It relies on a unique combination of a susceptible yolk sac transporter orientation and extreme, oral bolus doses that saturate maternal clearance pathways. Because human developmental physiology and MCT transporter expression patterns align with the insensitive rabbit model regarding early placental transport, the rodent findings cannot be reliably translated to presume any human relevance of adverse rodent developmental findings.

This was already acknowledged in previous evaluations by other non-European regulatory bodies (i.e. UK, Canada, and U.S.) [14-16]. However, also in EU, previous assessments on ethylene glycol were supportive of a non-classification. In 2015, ethylene glycol was prioritised via automatic screening. The Hungarian authorities accepted the justification for non-classification and agreed that classification for developmental toxicity was not warranted. Also, ethylene carbonate (CAS no. 96-49-1) was subject to regulatory evaluation in 2018. As ethylene carbonate is metabolised in vivo to ethylene glycol and CO_2, the reproductive toxicity data gap was addressed via read-across to ethylene glycol. Under the Community Rolling Action Plan (CORAP, 2018; Latvia), potential concerns were raised regarding reproductive toxicity and its wide-dispersive use. However, the provided justification addressing these concerns was ultimately accepted.

Since then, no major new data has been generated. Moreover, although numerous poisoning cases are described in the literature, no epidemiological evidence links ethylene glycol to developmental toxicity, despite its broad use in consumer products. To further substantiate the interspecies differences between rodents on the one hand and rabbits and humans on the other, the currently available PBPK model for rat and

human will be refined by incorporating an embryonic compartment. In addition, the model will be expanded to include the rabbit as an extra species. The Cefic EO Glycol Sector Group is currently engaging with modelling experts to update the PBPK model.

We respectfully request that the Subcommittee re-evaluates the weight-of-evidence under CLP criteria and removes the Category 1B (H360D) classification for prenatal developmental toxicity for ethylene glycol.

We remain at your disposal should the committee require additional clarifications or further supporting toxicokinetic data.

Sincerely,

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