Comments from REACH registrants

The Gezondheidsraad kindly contacted the REACH registrants of the above substance and offered them the opportunity to submit comments on the draft re-evaluation of 2-(2-methoxyethoxy)ethanol (DEGME - document dated 18/7/16). This response represents the collected comments from the following companies:

- INEOS nv
- Clariant
- BASF

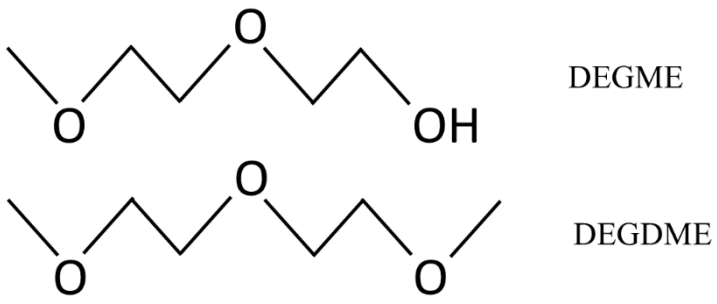
Identified Uses (page 11, section 3.2)

2-(2-methoxyethoxy)ethanol (DEGME) is much less widely used than in the past. It's primary remaining uses are as an intermediate or industrial processing aid and as an anti-icing additive in aviation kerosene. Use in coatings has declined substantially, remaining only in specialist industrial markets and in professional uses such as specialist printing inks and textile dyes. These uses are small in volume. The REACH joint registration specifically recommends against use in products for the consumer market.

Toxicokinetics (section 4.)

Some inaccurate data has been cited in this section of the document.

Line 15, page 12: Whilst DEGDME (diethylene glycol dimethyl ether) is structurally related to DEGME, it is in our view not appropriate to use it as a surrogate to predict the metabolism of DEGME. The structures of the two substances are shown below:



Crucially, it can be seen that there is a difference in the functional groups of the two substances. DEGME contains ether linkages and a terminal hydroxyl group. DEGDME contains only ether groups. The OH group is much more labile and opens up the opportunity for metabolism via alcohol and aldehyde dehydrogenase to form 2-(2-methoxyethoxy)acetic acid. DEGDME, or methyl diglyme, is a much more stable compound and only contains ether linkages. Metabolism at these sites is possible by dealkylase alone.

The metabolic pathway for DEGDME is shown in the diagram below. Data from Cheever (1988) and Daniel (1991) show that the principle metabolic pathway is via O-demethylation with subsequent oxidation to produce 2-(2-methoxyethoxy)acetic acid; this pathway is shown with the blue arrows. There are two sites in the molecule open to O-demethylation. In order to produce methoxyacetic acid as a metabolite, the central ether linkage needs to be broken. This is a sterically less available site and hence this is a minor pathway. Nevertheless, according to Cheever, this route accounts for nearly 10% of DEGDME metabolism leading to significant generation of methoxyethanol and hence, by oxidation, methoxyacetic acid. The data form Cheever also show that the relative importance of the different metabolic pathways is little affected by substrate concentration. This leads to the result that DEGDME is reprotoxic when tested in animals, as are all of the methyl glymes, due this metabolic process which yields the known reprotoxic substance methoxyacetic acid.

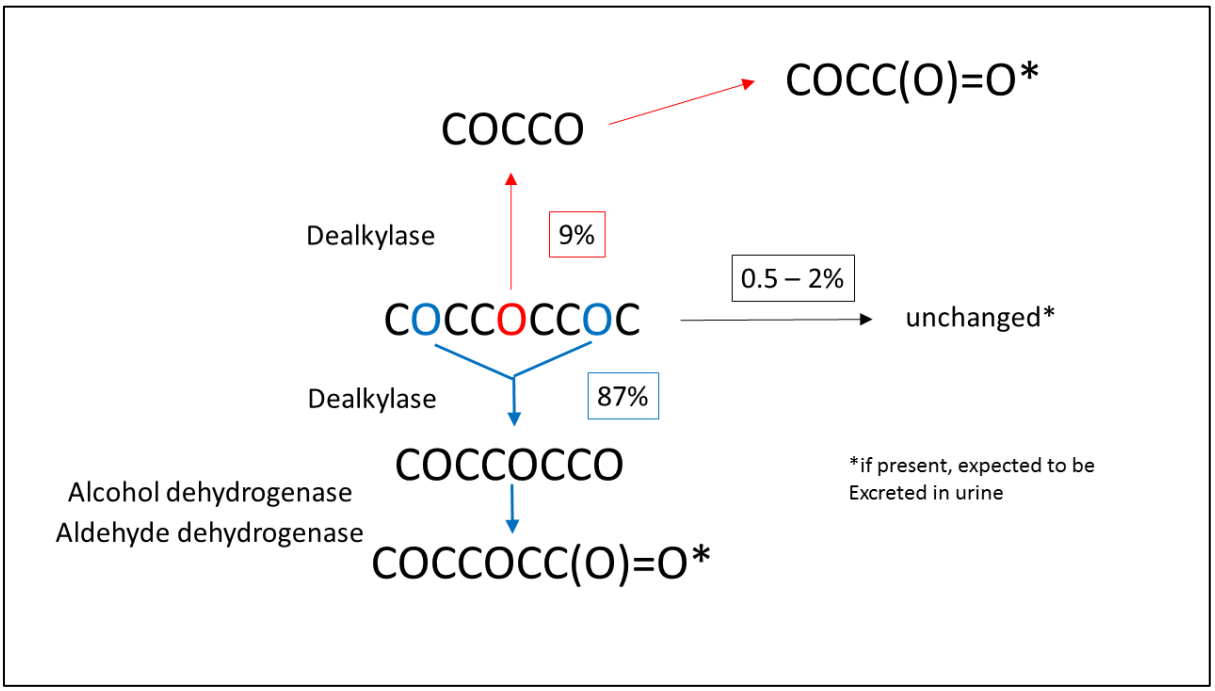
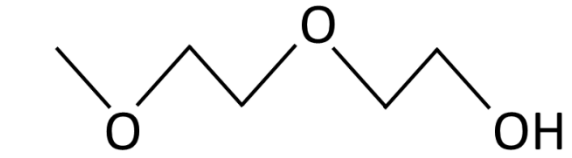
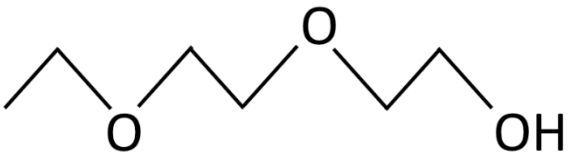


Figure 1: Measured metabolic routes for DEGDME. The 96h urinary metabolic profile as discussed in Cheever et al (1988) is shown as a percentage. Each number is the sum of all metabolites present in this specific metabolic pathway. DEGME is detectable in urine, but only at very low levels showing that it is rapidly oxidised when formed.

The presence of a hydroxyl group in the DEGME molecule provides a much more reactive site for metabolism. There is no published data on the metabolism of DEGME. However, a good surrogate to provide quantitative evidence is the closely related substance 2-(2-ethoxyethoxy)ethanol (DEGEE), which similarly shares the same number of ether and hydroxyl groups in its molecule and differs only in the length of the terminal alkyl chain group by one methylene unit (see the following diagram):



DEGME



DEGEE

There is privately held data for DEGEE (available in the REACH registration dossier of DEGEE) from a modern GLP study in which rats were orally dosed with radiolabelled DEGEE that shows the metabolite distribution to be as shown in the table below (Gattefosse, 2003). In this study, four rats were given a single oral dose of 1000mg/kg and the metabolites determined at 0.75 and 24 hours after dosing (2 animals sacrificed at each time period.)

Urinary metabolite identified	**Percentage of dose given in urine**
2-(2-ethoxyethoxy)acetic acid	75
2-(2-ethoxyethoxy)ethanol	3
Diethylene glycol	5
Unidentified 1	5
Unidentified 2	3

More than 90% of the applied dose was accounted for in urine in the first 24 hours. This data shows that the dominant metabolic pathway is oxidation of the hydroxyl group to carboxylic acid. More importantly, neither of the unidentified peaks was ethoxyacetic acid. In blood plasma, only 2-(2-ethoxyethoxy)ethanol and 2-(2-ethoxyethoxy)acetic acid were identified. This provides clear evidence that metabolism of DEGEE at a dose of 1000m/kg does not produce detectable levels of ethoxyacetic acid. It is reasonable to extrapolate that for DEGME the result would be similar and that metabolism to methoxyacetic acid would not occur to any detectable extent.

There is some additional albeit old data available to support this metabolic pathway. Fellows (1947) identified increased glucuronic acid (glucorinides) in urine following exposure of rabbits to DEGEE, although levels were low (typically <1% of ingested dose). Kammerling (1977) also confirmed that the acid 2-(2-ethoxyethoxy)acetic acid is a major metabolite.

By extrapolation of the measured metabolism data for DEGEE to DEGME, the following quantitative metabolic pathways would be expected:

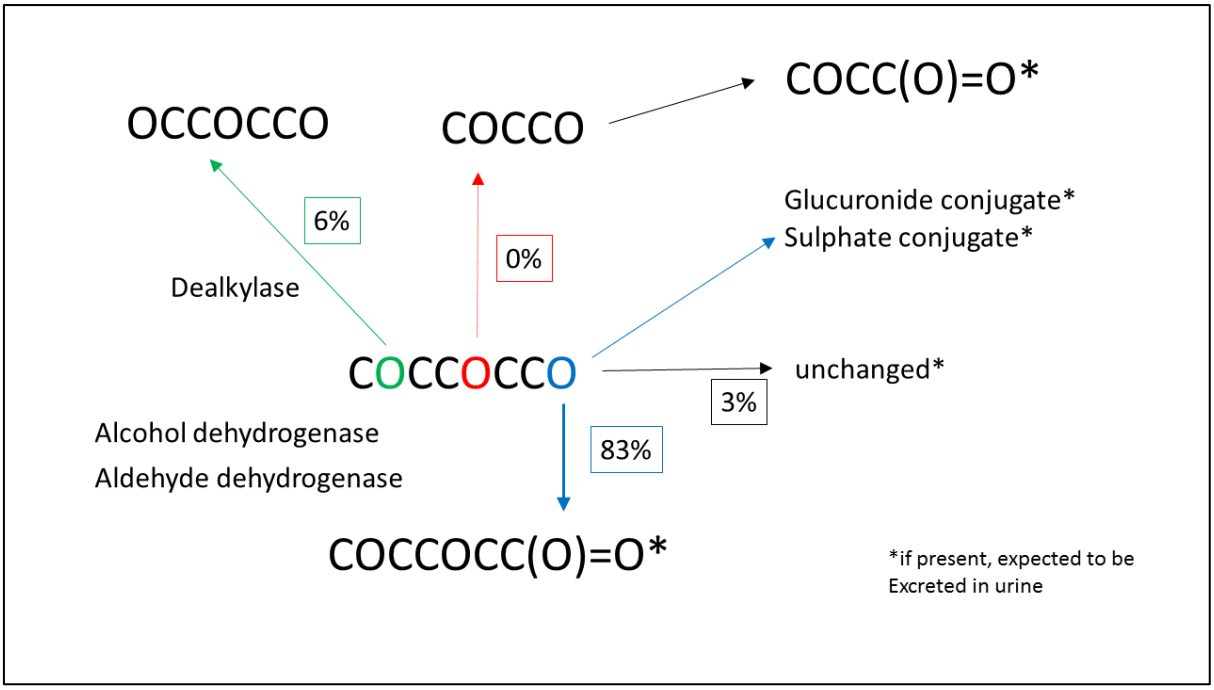


Figure 2: Probable metabolic routes for DEGME based on measured data for DEGEE. Percentages are of metabolites measured in urine. O-demethylation is a minor pathway. The unaccounted for metabolites are likely to be glucuronide or sulphate conjugates

This shows that the direct oxidation to methoxyethoxyacetic acid is the dominant pathway and that O-demethylation, which is the most significant route open for metabolism with DEGDME is a minor route for DEGME. The minor but significant metabolic route that can lead to methoxyacetic acid in DEGDME metabolism is just not seen in the alkoxyethoxyethanol, based on the evidence from DEGEE.

In conclusion, it is scientifically inaccurate to read across to DEGDME because this substance does not share the same function groups as DEGME (missing labile hydroxyl functionality) and therefore the same metabolic pathways. This is important when it is the metabolites that are responsible for toxicity. It is more appropriate to read across to the substance DEGEE, which shows that cleavage of the middle ether group does not occur to a detectable extent and that metabolism to methoxyacetic acid should not be a concern. Whilst, in the absence of a specific in vivo metabolism study on DEGME, the presence of MAA cannot be ruled out entirely, the evidence from DEGEE suggests that it is unlikely as a metabolite. We request that the Gezondheidsraad reconsiders its conclusion (page 12, paragraph line 33) in the light of this additional information.

Fertility toxicity data (page 14 onwards)

In both sections 5.1.3 and 5.3, reference is made to the toxicokinetics section reporting that both (2-methoxyethoxy)acetic acid and 2-methoxyethanol are metabolites of DEGME. As discussed above, 2-methoxyethanol is not expected to be a metabolite, based on the evidence from DEGEE. Therefore, we request that the Gezondheidsraad reconsiders this paragraph in the light of its reference to the reproductive classifications of both EGME and MAA.

Developmental toxicity data (page 18 onwards)

We agree that there is data indicating possible developmental toxicity but this is only seen to any significant extent at very high doses. Such developmental effects also need to be considered in terms of the associated maternal toxicity.

Maternal toxicity

In the Hardin (1986) range finder study, the doses assessed were 0, 1000, 1495, 2235, 3345 and 5175mg/kg. The top dose proved fatal to 2 of the 9 animals in this group. 3345mg/kg caused a significant (18%) reduction in maternal body weight by day 21 and a significant reduction in food consumption during days 7-12 (-22% compared to controls). Hence the two doses used in the main study were 720 and 2165mg/kg. However, the latter still caused significant maternal toxicity with a statistically significant (7%) reduction in maternal body weight by day 21 and a statistically significant reduction in food consumption during days 7-12 (9% reduction compared to controls).

Yamano (1993) carried out range finder studies with both pregnant and non-pregnant rats. In the non-pregnant rats, urinary pH turned acidic even at the lowest doses (control pH 8.0-8.5, 125mg/kg pH 7.0-8.0, 4000mg/kg pH 5.0-6.0). It can be presumed from knowledge of the metabolism, that this was due to the main metabolite, which may well also cause metabolic acidosis, based on the evidence from 2-butoxyethanol (EU, 2006). The doses of 3000 and 4000mg/kg also produced statistically significantly adverse effects on blood parameters, although the trend of reducing RBC, WBC, Hb and Ht concentrations was evident from 1000-2000mg/kg onwards. In the main study, the doses used were 0, 200, 600 and 1800mg/kg from GD7-17. In the high dose group, there was a statistically significant reduction in maternal body weight gain (6%), food consumption (15% on day 11) and thymus weight (21%), although the authors pointed out that the former could be due to decreases in the number and weight of foetuses. It is reasonable to assume that the urine pH would have been significantly reduced in the high dose group to below 7.

In the rabbit study of Scortichini (1986), there were again clear signs of maternal toxicity in the top dose used (750mg/kg). Of the parameters reported, these included a marked reduced body weight gain, which at certain periods was actually an absolute weight loss. Weight gain was only around 50% of control animals over GD6-28. There were also significant adverse changes to blood parameters (eg reduction in RBC by 7%).

The findings of maternal toxicity are consistent with the oral repeat dose toxicity studies that are available for DEGME. Kawamoto (1990) exposed male Wistar rats p.o. for 20 days to doses of 500, 1000 and 2000mg/kg. The study also looked at temporal effects by using a dose of 2000mg/kg for dosing periods of 1, 2, 5 and 20 days. The observed NOAEL in the 20 day study was 500mg/kg/day. At 1000mg/kg there was a significant reduction in relative thymus weight. At 2000mg/kg there was significant toxicity manifest as statistically significantly reduced body weight growth and reduced relative organ weights for at least one time point for the liver, kidney, spleen, thymus and testis. Krasavage (1983) exposed male CD rats by oral gavage to doses of 900, 1800 and 3600mg/kg for 6 weeks. The observed NOAEL was 900mg/kg. The high dose group produced significant reductions in body weight gain and feed consumption. These effects were also manifest in the mid dose group to a lesser extent. The high dose group also showed slight but significant changes to clinical chemistry (BUN elevation). There were statistically significant changes to relative heart and liver weights in the mid dose group and in the high dose group, as well as for these two organs, significant changes were seen in the relative weights of the kidney (elevated), spleen and testes (reduced). Testicular atrophy was noted at 3600mg/kg, with adverse histopathological changes also seen.

Hermsen et al (2011) used the Zebrafish Embryotoxicity Test to examine the developmental toxicity potential of a number of glycol ethers. They used a novel quantitative evaluation method to assess the development of the zebrafish embryo based on specific endpoints in time, the general morphology score (GMS) system. For teratogenic effects a separate scoring list was developed and used. They assessed the acid metabolites methoxyacetic acid (MAA), ethoxyacetic acid (EAA), phenoxyacetic acid,

butoxyethoxyacetic acid, methoxyethoxyacetic acid and the parent glycol ethers of the first two, i.e. methoxyethanol and ethoxyethanol. Only MAA and EAA resulted in a concentration dependent decrease in GMS. The other glycol ether metabolites did not reduce the GMS as compared to the controls up to the highest concentration that could be tested without causing general toxicity. Embryos exposed to MAA and EAA showed comparable dysmorphology after exposure; several teratogenic effects were observed following exposure to these substances, among which heart, head and tail malformations (characteristics seen in mammalian developmental toxicity tests), were the most pronounced. Unlike their metabolites, the parent compounds EGME and EGEE did not show any effect on general morphology and teratogenicity. No effects were seen with the other glycol ethers. This data shows that methoxyethoxyacetic acid (the main metabolite of DEGME) does not share the developmental toxicity potential of methoxyacetic acid.

Overall, at doses in excess of 1000mg/kg, there does appear to be clear signs of maternal toxicity in rats, manifest by reduced weight gain and food intake, reduced organ weight and adverse changes to blood parameters. Acidic urine is also seen and could be an indicator of possible acidosis of the blood. Acidosis is developmentally toxic and therefore the developmental effects may be secondary to the expected acidosis. In rabbits, there are clear signs of maternal toxicity at the top dose tested, manifested as severely reduced body weight gain and adverse blood parameters. Developmental effects associated with these changes need to be interpreted with care as they may be secondary to general maternal toxicity.

Other considerations of doses used

The studies available would have been carried out to old protocols which took less account of animal welfare issues and the need to limit maximum doses used. All modern test protocols have an implicit maximum oral testing dose of 1000mg/kg, specified as an accepted single dose for a limit test. These include all modern protocols for reproductive toxicity testing. Testing above these limits is normally only required if expected human exposure is expected at high doses; clearly not the case for DEGME. For this reason, it is instructive to filter the data as if it was generated to current criteria, with oral dosing limited to 1000mg/kg. In this case, the dataset would look like this:

Study [species - route]	**Test doses (n=animals/dose)**	**Results (statistically significant effects)**
Hardin (1986) range finder study [SD rat - gavage]	0, 1000mg/kg (n=9)	No statistically significant adverse effects seen[1]
Hardin (1986) full study [SD rat - gavage]	0, 720mg/kg (n=12/13)	'Total rib' malformations (15/111) Variations – reduced ossification – cranial (10/111) and appendicular skeleton (6/111). Lesions also occur spontaneously in controls albeit at lower incidence. [2]
Yamano (1993) range finder study [Wistar rat – gavage]	0, 125, 250, 500, 1000mg/kg (n=4-6)	No adverse effects seen but no gross or histopathology carried out.
Yamano (1993) full study [Wistar rat – gavage]	0, 200, 600 mg/kg (n=14)	Effects only in high dose: Reduced foetal weight (~20%). Variations: thymic remnant in the neck (unilateral) (20/98). [Reduced incidence at 1800mg/kg (8/59)] Only one incidence in control rats. Degree of ossification is affected.[3]
Doe (1984) [rat – subcutaneous]	0, 255, 510, 1020mg/kg (n=15) –	No adverse effects seen, but no

	all dose groups	gross or histopathology carried out.
Schuler (1984) [mouse – gavage]	Only dose group is 4000mg/kg so study drops out of comparison using the 1000mg/kg cut off.	
Scortichini (1986) [rabbit – dermal]	0, 50, 250, 750mg/kg (n=25) No filtering as this is a dermal study, but all doses are below 1000mg/kg anyway.	250mg/kg: Cervical spur of vertebrae (17/194) and delayed ossification of hyoid skull (57/194)**. 750mg/kg: Maternal effects (reduced bw gain, GD9-11 – actually weight loss, reduced RBC and PVC (~7%). Fetal effects as for 250mg/kg plus mild forelimb flexure (29/68)*, dilated renal pelvis (8/68), retrocaval ureter (6/68), delayed ossification of sternebrae (93/120)**. [4] *seen in control rabbits - ** seen at high incidence in controls.

Non-statistically significant findings that may be biologically significant.

1.One pup at 1000mg/kg showed multiple cardiovascular malformations. None were seen at 1495mg/kg, although the number of litters examined was lower. Incidence increased at doses above this, although not significantly until the top dose, when there was also clear evidence of maternal toxicity.

2. It was noted that one pup had a ventricular septal defect at 600mg/kg with a much higher incidence at 1800mg/kg.

3. It was noted that one pup had a ventricular septal defect at 720mg/kg with a much higher incidence of multiple cardiovascular malformations at 2165mg/kg.

4. Single ventricular septal defect seen in low dose group – observation regarded as spontaneous and neither significantly nor biologically significant.

The Doe study did not involve any gross or histopathology, so is not complete as a developmental toxicity study, hence there are only three studies on which to comment on once the 1000mg/kgbw/day 'filter' is applied: Yamano, Hardin and Scortichini. As can be seen from the above table, once a dose ceiling is imposed, the evidence supporting significant adverse effects becomes very limited. The full study by Hardin showed only malformations in the ribs, and then only when two individual findings, neither significant on their own, were added together; one of these (wavy ribs) is regarded as a variation of low to moderate concern (ECETOC, 2002). Note that these findings were not seen in the Hardin range finder study at 1000mg/kg. The range finder is statistically less powerful but the number of animals used was not that many fewer (9 in the range finder versus 12/13 per dose in the full study). This throws some doubt on whether this effect is reproducible at this dose. The Yamano study, using a different rat strain, showed reduced foetal weight and some slight additional variations. None of the findings were repeated across the two studies by Yamano and Hardin, which again must raise questions over how repeatable these effects are at doses below 1000mg/kg. In the rabbit study (Scortichini), there was evidence for excessive maternal toxicity at the top dose, so the effects at 250mg/kg are of main interest. These were limited to two variations, one of which was prevalent at a significant rate in the controls. Such effects are normally rated to be of low to moderate concern (ECETOC, 2002).

In section 5.4.3, reference is made to methoxyacetic acid, as an assumed metabolite of DEGME. As mentioned earlier, metabolism studies on a similar substance have shown that this may not be the case. Therefore, we request the Hoge Gezondheidsraad to reconsider this paragraph in the light of its reference to EGME and MAA as substances classified for effects on development (Repr Cat 1B).

Comparisons with the CLP criteria (page 25)

We would like to comment point by point on the conclusions made by the Hoge Gezondheidsraad:

Hoge Gezondheidsraad statements	Comment to challenge
Page 25, line 14: "In several species, severe developmental effects were reported (i.e. reduced fetal viability in rats, mice and rabbits; increased visceral malformations in rats)."	This is true but only at high doses well in excess of 1000mg/kg, the upper limit used in modern test protocols. The effects seen at doses at or below this were limited to a small number of mild to moderate effects regarded primarily as variations. We believe it is unreasonable to describe effects seen in old studies at very high doses well above 1000mg/kg as severe without making this dose issue clear. It is also not made clear in this section that there was evidence for maternal toxicity in the highest dose groups in all of the studies examined and especially at doses exceeding 1000mg/kg.
Page 25, line 16: "In two studies with rats, specific and severe developmental effects have been reported in rats, that show a dose-response relationship. These responses were observed at relatively high doses (≥1800 mg/kg bw), at which also effects on maternal body weight and possibly a reduction in Hb occurred. The Committee notes that it is not clear whether the reduction in maternal body weight is a direct effect or an indirect consequence of the observed reduction in foetal viability."	We agree with the point made and the statement does acknowledge that effects were at high dose and maternal toxicity may have played a causal role in the observations seen. However, we believe it should be re-enforced that effects below current limit test threshold of 1000mg/kg were primarily restricted to an increase in variations that are both seen in controls that were only just statistically significant, plus that these effects were not consistently repeated either between studies or within studies between the range finder and the main study.
Page 25, line 22: "The relevance of the developmental effects for classification should therefore be assessed (CLP criteria 3.7.2.5.7 and 3.7.2.5.9). In this regard, the Committee considers the cardiac malformations (malformations of the aortic arch; ventricular septal defects) of particular interest as these are generally not associated with maternal toxicity in rats."	These effects were not seen at significant levels at doses at or below 1000mg/kg. They were only seen at doses of 1800mg/kg and above. They were not seen in the Hardin range finder study at a dose of 1495mg/kg (although the number of litters examined was only half those of the lower dose, which does reduce the power of detection). They were only seen in a single fetus in the Yamano study at a dose of 600mg/kg. It is plausible that these effects could be a secondary consequence of metabolic acidosis from the acid metabolites, which would correlate with the reduced pH of urine. Whilst we acknowledge that there are other potential causes of reduced pH and that metabolic acidosis is not the only cause of heart and blood vessel malformations, this explanation cannot be excluded. In the interests of transparency, we believe this should be made clear. The fact that there were no significant findings at doses below

	1000mg/kg and would therefore not be seen if tested to a modern protocol should make these observations of lesser importance.
Page 25, line 25: "In addition, malformations of the heart (dilated ductus arteriosus and dilated aortic arch) have been reported after exposure to 2-methoxyethanol (at 158 mg/kg bw/d and higher) and 2-methoxyacetic acid (at 186 mg/kg bw/d and higher). These substances are, based on data available on glycol ethers, expected metabolites of DEGME. Both 2-methoxyethanol and 2-methoxyacetic acid are classified in Category 1B for developmental toxicity".	The available data as presented in this document suggests that methoxyethanol and hence methoxyacetic acid would not be expected as significant metabolites of DEGME at doses up to 1000mg/kg*. DEGDME is not an appropriate source substance from which to predict the toxicology of DEGME as it quantitatively follows different metabolic pathways due to the lack of hydroxyl functionality. A better surrogate is DEGEE, for which data shows the monoalkoxyacetic acid is not a detected metabolite at a dose of 1000mg/kg. The lack of reprotoxicity of DEGEE also confirms that this metabolic pathway is of no importance for this substance. If it were to be then DEGEE would break down to ethoxyacetic acid, which is known to be a developmental toxicant.
Page 25, line 32: "The Committee, furthermore, considers that severe developmental effects have been observed at lower doses, at which no maternal toxicity was observed. One malformation of the aortic arch and one ventricular septal defect were observed, at dose levels at which no maternal toxicity was observed."	In our opinion, this overstates the evidence, particularly for effects at doses up to the current testing limit normally used of 1000mg/kg. In the Hardin main study there was one pup (out of 115) with a malformation of the aortic arch at 720mg/kg. In the range finder study, one pup of 38 exhibited multiple heart defects at 1000mg/kg but none at 1495mg/kg (albeit with the latter observation from a smaller group size). In the Yamano study there was one pup with a ventral septal defect at 600mg/kg. None of these findings were statistically significant. We do not believe that these findings constitute severe effects *at doses up to 1000mg/kg*.
Page 25, line 37: Finally, existing evidence indicates that 2-methoxyethanol and 2-methoxyacetic acid are eliminated more slowly in humans than in animals. This suggests that in humans, developmental effects might occur at lower external exposure levels than in rats.	On the basis of the above comments, if 2-methoxyethanol is not a significant metabolite, then this observation would not be relevant. If the Hoge Gezondheidsraad accept our earlier comments then it would be appropriate to delete this section.

*It is a possibility that at doses in excess of 1000mg/kg, especially in the rat studies that were all by oral gavage, that the active metabolic routes identified for DEGEE could become saturated, even if only for the immediate period after dosing, leading to the metabolic route to MAA becoming active. Such a hypothesis would both explain the effects seen at high dose and the lack of formation of EAA from DEGEE metabolism at 1000mg/kg and no reproductive effects below 1000mg/kg.

Conclusions

In conclusion, we do not believe that there is sufficient strength of evidence to justify a classification of category 1B for reprotoxicity. Evidence from a structurally more closely related glycol ether than a

glyme suggests that this substance would not metabolised to the known reproductive toxicant methoxyacetic acid in significant amounts up to doses of 1000mg/kg. Therefore classification decisions should be based solely on the strength of the toxicity data. At doses at or below 1000mg/kg, the limit used for modern test protocols, the evidence for developmental toxicity is limited and compromised by maternal toxicity. Some effects do bear a biological similarity to those seen with methoxyethanol at much lower doses, but it should be emphasised that these are weak and none reach biological significance at doses below 1000mg/kg (and indeed only reach significance at doses well above this) and the effects at lower doses (<1000mg/kg) could plausibly be secondary to other maternal toxicity. A few effects are seen at doses below 1000mg/kg, but taking into account that they are:

- Only just statistically significant
- Are increases in the rate of lesions seen in control animals
- Are mainly lesions that are regarded as variations of low to moderate concern

We believe there is sufficient uncertainty that current classification of category 2 is appropriate. The data does not appear to be sufficiently convincing for a category 1B classification.

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