Mrs. K. Smet
INEOS Oxide

Gezondheidsraad
Health Council of the Netherlands

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| Date: | November 21, 2017 | Your ref: | Email, dated October 18, 2016 | E-mail: | sr.vink@gr.nl |
| Encl: | | Our ref: | 1257124/SV/cn/543-B17 | Phone: | +31 6 527 81 584 |

Subject: Comments on draft report *2-(2-Methoxyethoxy)ethanol (DEGME)*

Dear dr. Smet,

Thank you for accepting the invitation to comment on the draft report 2-(2-Methoxyethoxy)ethanol (DEGME), which was published for public review in July 2016 by Subcommittee on the Classification of Substances Toxic to Reproduction, a committee of the Health Council of the Netherlands. The Committee expresses its appreciation for the thorough review of the draft report. In addition, the Committee thanks INEOS for providing the results of a metabolism study on DEGME. The response of the Committee is outlined in this letter.

In your commentary letter, on behalf of INEOS, Clariant and BASF (further referred to as INEOS), it is argued that the read-across that was described in the draft report (i.e. from DEGDME to DEGME) was not justified. The Committee agrees with INEOS' comments on the read-across applied. Importantly, after the public review a metabolism study has been conducted and the results have been made available to the Committee. Therefore, the use of read-across is no longer indicated. The sections of the report referring to read-across have been updated based on the new data. The Committee will therefore not further address the comments made regarding conclusions on the metabolism of DEGME based on read-across.

Besides the read-across applied, the comments of INEOS mainly concerned considerations on (1) possible maternal toxicity, (2) the doses DEGME applied and (3) the severity of the developmental effects observed. INEOS points to the literature in which maternal toxicity has been observed, which include a reduction in body weight, reduction in thymus weight, adverse effects on blood parameters, and possible acidosis.

The Committee is of the opinion that specific developmental effects should not be ignored (exclusively) based on limit dose considerations. It considers the occurrence of the cardiac malformations (malformations of the aortic arch; ventricular septal defects) in rats not causally related with the maternal toxicity reported. The Committee notes that cardiac malformations have also been observed in rats at doses below 1000 mg/kg bw/d. One malformation of the aortic arch and one ventricular septal defect were observed at 720 and 600 mg/kg bw/d, respectively. Although not statistically significant at these dose levels, the Committee considers these effects suggestive of a dose-response relationship, and are therefore considered severe effects. Overall, the Committee considers a proposal for a classification in Cat. 1B warranted. The considerations of the Committee have been clarified in the report.

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In response to your commentary letter, textual changes have been also been made concerning the use of DEGME, and the inconsistency of the increase in variations observed in the studies by Hardin et al. and Yamano et al.

In the accompanying e-mail you can find a link to a copy of the final report on DEGME.

Yours sincerely,

S.R. Vink, PhD
Scientific secretary