

Industry's position on the recent publication by Cherry et. al. on male infertility and glycol ether exposure.

Background

Recently an article was published in the scientific journal "Occupational and Environmental Medicine" (OEM) claiming an association between male infertility and glycol ethers. The conclusions were based on an epidemiological case-control study. The study compared 874 men with low sperm motility with 1244 men with normal sperm motility. A standard questionnaire was used to collect information on factors that were thought to influence male infertility. Amongst others these factors included exposure to glycol ethers. Industrial hygiene experts classified the subjects according to their exposure status based on the responses provided in the questionnaires. The article concluded that it provides an indication for a weak association between glycol ether exposure and male infertility.

Industry's position

The article in OEM revealed a number of shortcomings, which are listed below:

1. **Exploratory character of the study.** Although the publication mentions that the study was specifically focused on glycol ether exposure, this was not the case. The study was launched to investigate a range of factors that may contribute to male infertility of which solvent exposure including glycol ether exposure was only one. Studies that do not focus on one specific association are regarded to be less valuable from a scientific point of view.
2. **Overall association between glycol ethers and male infertility.** The study does not show an overall association between any glycol ether exposure and male infertility. The only statistically significant finding relates to the category of "high" exposure and barely reached a level of statistical significance.

3. **Extremely poor agreement between exposure assessors.** Two experts independently evaluated the exposure information from the study subjects. Rater 1 classified 29 subjects as highly exposed, whereas rater 2 only classified 6 as highly exposed. Only 2 subjects were rated as highly exposed by both. The extremely poor agreement between the exposure assessors indicates that the exposure classifications are not reliable and of too questionable quality to draw firm conclusions from.
4. **Biomonitoring data do neither confirm exposure nor the association.** As a separate part of this study blood and urine samples were collected from all study participants. The samples from all subjects classified as highly exposed to glycol ethers, 56 out of the 129 in the category moderately exposed and a selection of the other subjects were analyzed to confirm exposure to glycol ethers. Metabolites indicating exposure to glycol ethers could only be detected in 10 samples. In fact there was an inverse relationship between a positive urine sample and male infertility, suggesting a lower infertility prevalence in persons with glycol ether exposure. Industry believes that the information from the questionnaires as well as the exposure information based on the urine samples should be consistent before any firm conclusions can be drawn.
5. **Incorrect time window of exposure.** The study only used exposure information from the questionnaire for the three months immediately preceding the fertility checkup. This may seem a logical step, but all couples had to be attempting to conceive at least one year before being eligible to the study. This means that infertility was already present nine months before the period for which the exposure information was collected.

Conclusion. Industry experts reviewed the recently published article reporting an association between male infertility and glycol ether exposure. They identified a number of serious shortcomings in the publication. Although several of these shortcomings were described in a study report submitted to the sponsors of the project they were not included in the scientific article in OEM. The shortcomings pertain to critical aspects of the study and raise serious concern about the published findings.