

NTP Research Concept: Ethylene Glycol 2-Ethylhexyl Ether

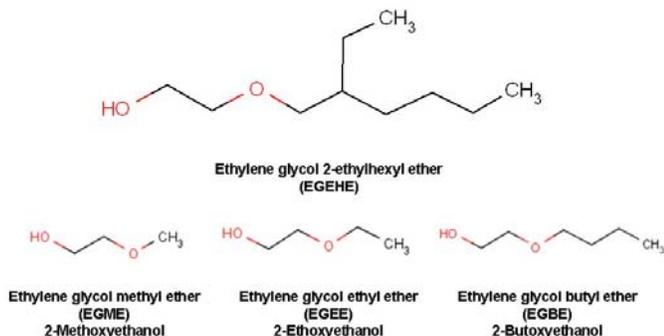
Project Leader

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Background and Rationale

Ethylene glycol 2-ethylhexyl ether (EGEHE) was nominated by NIEHS for toxicological characterization due to its widespread use, unknown toxicity profile, and structural similarity to other known toxic ethylene glycol ethers. EGEHE is a solvent used in paints, special coatings,

polishes, lacquers, and inks. US production of EGEHE has been increasing since 1990 and was greater than 1 to 10 million pounds in 2002. Routes of exposure, which have not been assessed, may be through inhalation and dermal contact similar to the other ethylene glycol ethers. EGEHE's vapor pressure is considerably lower than the other ethylene glycol ethers suggesting vapor inhalation may not be a major route, but exposure to aerosols may occur.



Currently only acute (LD₅₀) data is available for EGEHE. The NTP has not conducted EGEHE studies, but has studied other glycol ethers. Subchronic studies via drinking water of ethylene glycol methyl ether (EGME), ethylene glycol ethyl ether (EGEE), and ethylene glycol butyl ether (EGBE) showed EGME and EGEE are testicular toxicants, which is consistent with previous literature. All three glycol ethers were hematotoxic, which again is consistent with the previous literature. EGME affects red and white blood cell numbers, while EGEE and EGBE target red blood cells. Female rats were found to be more sensitive to EGBE's hematotoxic effects than the males, which is likely due to a slower excretion rate in females. Several of the glycol ethers have been examined for reproductive effects, and reported that alkyl length was inversely related to potency. EGME and EGEE are developmental toxicants. Gestational exposure to these compounds results in skeletal and soft tissue malformations in animal studies of several species. Unpublished data from a subchronic exposure study indicate that EGEHE may have reproductive and erythrocyte toxicity.

Table: Summary of known toxicities of Ethylene Glycol Ethers and relative potencies:

Toxicity	Ranking
Testicular	EGME > EGEE
Development	EGME > EGEE
Erythrocyte	EGBE > EGEE > EGME
Leukocyte	EGME > EGEE

Structurally similar to other ethylene glycol ethers, EGEHE may be oxidized to an aldehyde by cytosolic alcohol dehydrogenase and then to an alkoxyacetic acid by aldehyde dehydrogenase. The alkoxyacetic acid metabolites of EGME, EGEE, and EGBE are the most abundant metabolites and are responsible for inducing their particular toxicities.

EGME, EGEE, and EGBE and their corresponding metabolites were mostly negative for mutagenicity in Salmonella assays except for EGBE and the EGME aldehyde metabolite at high doses. The NTP chronic EGBE exposure study (via inhalation) reported some evidence of carcinogenicity based upon increased hemangiosarcomas in male mice and increased squamous cell papillomas within the forestomach of female mice. Uncertain findings in male mice were the increase in heptacellular carcinomas and marginal increase in forestomach squamous cell papillomas. There was no evidence of carcinogenicity in male rats and equivocal evidence in female rats based on the incidences of pheochromocytomas.

Key Issues

The acute toxicity data for ethylene glycol 2-ethylhexyl ether does not adequately address subchronic or chronic toxicity questions especially those of potential testicular toxicity, developmental toxicity, hematotoxic activity, and carcinogenicity. The reproductive and development effects are inversely related to alkyl chain length, which suggests that EGEHE may not have these effects. However, it is not known if EGEHE is metabolized to shorter alkyl ethylene glycol ethers or if the alkoxyacetic acid(s) metabolites are toxic. EGEHE may have similar toxic effects on erythrocytes that are displayed by the longer alkyl chain EGBE, which may result in anemia.

Proposed Approach

Conduct metabolism studies of EGEHE in rodents to determine if shorter chained glycol ethers and/or alkoxyacetic acids are generated *in vivo*. If EGEHE is metabolized into shorter alkoxyacetic acid metabolites, this would suggest that EGEHE is a testicular and developmental toxicant and further studies may not be needed. In addition to metabolism studies, absorption of EGEHE through various routes of exposure would be evaluated for comparison and provide guidance for dose route and selection for *in vivo* studies.

EGEHE may be metabolized to alkoxyacetic acids that have an unknown toxicity profile, which would require further investigation. The NTP would assess EGEHE toxicity after subchronic exposure. Endpoints evaluated during the course of these studies would include histopathology of the hematopoietic tissues and the testis, and hematology evaluation.

Data from the ADME and subchronic studies would provide guidance for the need and design of larger studies with longer exposure. Finding a hematotoxic response by

EGEHE may lead to immuno-toxicity studies, depending on the nature of the hematotoxic response (e.g. depleted lymphocytes). A reproductive assessment by continuous breeding (RACB) may be appropriate if evidence for reproductive effects arise such as histological effects in the testis. This study protocol would evaluate sex specific fertility issues after EGEHE exposure. A developmental toxicity study would also be considered due to the teratogenic activity of the other ethylene glycol ethers. Although the previously tested ethylene glycol ethers were negative for genetic toxicity, there was some evidence of carcinogenicity for the butyl form in mice. Carcinogenicity studies by an appropriate route would be considered following completion of the prior outlined studies.

Significance and Expected Outcome

Ethylene glycol 2-ethylhexyl ether is produced in large quantities and is structurally related to other glycol ethers that are testicular and developmental toxicants, affect hematopoietic tissues, and display some evidence of carcinogenicity in mice. These proposed studies would address the lack of toxicity data for EGEHE and provide hazard information for regulatory agencies and the public. In addition, these proposed studies may provide structure activity relationship data for the longer and branched alkyl chain ethylene glycol ethers, which to date consists mostly of toxicity data from the butyl form.

References

NTP Toxicity Report #26 "Toxicity Studies of Ethylene Glycol Ethers: 2-methoxyethanol, 2-ethoxyethanol, and 2-butoxyethanol". NIH Publication #93-3349, July 1993. Available at URL: <http://ntp.niehs.nih.gov/go/13823>

NTP Technical Report #484 "Toxicology and carcinogenesis studies of 2-butoxyethanol". NIH Publication #00-3974, March 2000. Available at URL: <http://ntp.niehs.nih.gov/go/9769>

[Reference and link to nomination pages, supporting documents, and study recommendations on NTP public web site (<http://ntp.niehs.nih.gov/go/nom>)]