

PEG 3350 Administration Is Not Associated with Sustained Elevation of Glycol Levels

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Objective To determine whether trace amounts of ethylene glycol (EG), diethylene glycol (DEG), or triethylene glycol (TEG) in PEG 3350 are associated with increased blood levels of EG, DEG, or TEG in children receiving daily PEG 3350 therapy.

Study design Blood samples were drawn from 9 children who were being treated for constipation with PEG 3350 (6-12 years old) before and every 30 minutes for 3 hours after receiving 17 g of PEG 3350. PEG 3350, tap water, and blood samples from 18 age- and sex-matched controls also were analyzed.

Results Baseline blood levels of EG and TEG did not differ between control and treated groups. DEG levels (median [IQR]) were lower in the PEG 3350 group (40.13 ng/mL [36.69, 63.94] vs 92.83 ng/mL [51.06, 128.93], $P = .008$). After PEG 3350 dose, levels of EG (390.51 ng/mL [326.06, 624.55]) and TEG (2.21 ng/mL [0, 4.5]) peaked at 90 minutes at 1032.81 ng/mL (826.84, 1486.13) ($P = .009$) and 35.17 ng/mL (15.81, 45.13) ($P = .0005$), respectively. DEG levels did not significantly change. Standard 17-g doses of PEG 3350 in 8 oz (237 mL) of water resulted in concentrations (mean \pm SD) of EG, DEG, and TEG of 1.32 ± 0.23 μ g/mL, 0.18 ± 0.03 μ g/mL, and 0.12 ± 0.01 μ g/mL, respectively. EG, DEG, and TEG levels in public water supply were 0.07 μ g/mL, 0.21 μ g/mL, and 0.02 μ g/mL, respectively.

Conclusions Daily PEG 3350 therapy in children was not associated with sustained elevation of EG, DEG, or TEG blood levels over levels in matched controls. Although EG and TEG levels increased after a standard dose of PEG 3350, their peak values remained well below toxic levels. (*J Pediatr* 2017;■■■:■■■-■■■).

Constipation is a common problem in children, accounting for 3%-10% of general pediatric clinic visits and up to 25% of referrals to pediatric gastroenterologists.¹ The worldwide prevalence of functional constipation varies from 0.7% to 29.6%, and this disorder occurs in all pediatric age groups.^{2,3} Constipation in children leads to estimated annual healthcare costs of \$3.9 billion in the US.⁴

Polyethylene glycol (PEG) 3350, a commonly used laxative approved by the Food and Drug Administration (FDA), is available over the counter. PEG refers to a family of organic polymers that use ethylene oxide as the base unit. PEG polymers are commercially available in molecular weights of 300 g/mol to 10 000 000 g/mol.⁵ The label on laxative compounds such as PEG 3350 refers to an average molecular weight of the included polymers.

Many medications approved for adult usage routinely are prescribed for children, PEG 3350 compounds included. PEG 3350 currently is approved for treatment of constipation in persons 17 years of age or older but frequently is used off-label in younger children. Since its introduction in the US in 1990, PEG 3350 is recommended over other treatment options for chronic constipation in pediatric population, based on its efficacy and ease of administration.^{6,7}

Recently, the safety of PEG 3350 in pediatric population has come under scrutiny. The FDA has received reports of neuropsychiatric events in children while taking PEG 3350, and a public summary from a Drug Safety Oversight Board Meeting on June 18, 2009, reported that neuropsychiatric events such as seizures, tremors, tics, anxiety, lethargy, aggression, paranoia, mood swings, and obsessive-compulsive behaviors such as repetitive chewing and sucking have been observed in patients receiving PEG 3350 for treatment of constipation.⁸ This list of neuropsychiatric events could be due to comorbid conditions that commonly occur in children with constipation.⁹ Indeed, it has been reported that behavioral problems are common in children with constipation and include aggression, anxiety, depression, and increased emotional reactivity.⁹⁻¹⁶ Furthermore, studies in animals indicate that constipation may lower seizure threshold.¹⁷

ATSDR	Agency of Toxic Substances and Disease registry
DEG	Diethylene glycol
EG	Ethylene glycol
FDA	Food and Drug Administration
GI	Gastroenterology
HPLC	High-pressure liquid chromatography
NCH	Nationwide Children's Hospital
PEG	Polyethylene glycol
TEG	Triethylene glycol

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In a FDA request for proposals to study whether PEG 3350 might contribute to these events (<http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-14-088.html>), it was reported that PEG 3350 might contain trace amounts of ethylene glycol (EG), diethylene glycol (DEG), and triethylene glycol (TEG). DEG and TEG are the smallest polymers of EG in that they comprise 2 and 3 units of EG, respectively. Although exposures to low levels of EG, DEG, TEG species are considered safe,¹⁸⁻²⁰ exposure to larger concentrations can be neurotoxic.^{20,21} The potential presence of these compounds in PEG 3350 raises concern as to whether EG, DEG, and TEG might contribute to neuropsychiatric adverse events in children. The purpose of this study was to evaluate whether EG, DEG, and TEG are found in the blood of children taking PEG 3350 at greater levels compared with children not taking PEG 3350. We also determined whether ingestion of a standard dose of PEG 3350 caused an increase in blood levels of EG, DEG, and TEG.

Methods

This study was approved by the Nationwide Children's Hospital (NCH) institutional review board (IRB14-00591). Children aged 6-12 years were recruited from the outpatient gastroenterology (GI) clinic at NCH. Those taking 17 g of PEG 3350 daily for more than 2 weeks for treatment of constipation and with no history of other GI disorders or abdominal surgeries (ie, inflammatory bowel disease, celiac disease, chronic intestinal pseudo-obstruction, Hirschsprung disease, or intestinal malrotation) that might affect intestinal motility or mucosal integrity were eligible for the study. Informed consent was obtained, and participants were scheduled for a morning visit before taking their daily dose of PEG 3350 (17 g). An intravenous catheter was placed in each participant to facilitate obtaining multiple blood samples. Each participant brought the bottle of PEG 3350 that they were currently using at home and measured out 2 doses. One dose was mixed in 8 ounces of tap water provided by a research nurse, and the other dose was stored for later analysis. A blood sample was drawn before the subject drank the morning dose, and subsequent blood samples were drawn every 30 minutes for 3 hours after the dose.

Control blood samples were obtained to assess background levels of EG, DEG, and TEG in the general pediatric population. Blood was obtained from 2 age- and sex-matched controls for each study participant. Samples were obtained from either excess blood that was to be discarded from the outpatient laboratories or from volunteers who responded to fliers that were mailed to families who previously agreed to participate in clinical studies at NCH. Control samples from the laboratory were obtained from patients whose charts indicated that the patient did not have constipation, other GI disorders, or previous abdominal surgeries and currently not taking any medications (prescribed or over the counter). Volunteers were allowed to give blood samples after a phone interview revealed they met same criteria.

To investigate the public water source used to mix the PEG 3350 for EG, DEG, and TEG, weekly random water samples

were obtained (n = 4) from the water source used in the outpatient clinic for the study.

Sample Analysis

A total of 100 μ L of plasma was spiked with ethylene-d₄-glycol as an internal standard (10 μ L of a 2 μ g/mL solution), and proteins were precipitated with trichloroacetic acid. After mixing, samples were placed on ice for 10 minutes and then centrifuged. The supernatants were collected, and 1 mL of high-pressure liquid chromatography (HPLC)-grade water and 200 μ L of 30% sodium hydroxide were added. Dibenzoyl glycol derivatives were formed by adding 40 μ L of benzoyl chloride and mixing thoroughly. Samples were extracted with 2 mL of hexane, and the organic layers were collected. The extraction was repeated, and the extracts were pooled, dried under a stream of N₂, and reconstituted in 100 μ L of 95% acetonitrile.

PEG laxatives were prepared at the stated therapeutic dose (17 g per 8 fluid oz of HPLC water, or 237 mL = 72 mg/mL). One milliliter was removed and prepared as described for the plasma samples. Samples of HPLC water were evaluated to confirm it did not contain EG, DEG, and TEG.

Levels of EG, DEG, and TEG were measured in plasma, stored samples of PEG 3350, and tap water by liquid chromatography–tandem mass spectrometry via multiple reaction monitoring. The samples were analyzed on an ABI/Sciex 4000 QTrap mass spectrometer (Sciex, Framingham, Massachusetts) equipped with a Shimadzu 20 series HPLC (Shimadzu, Columbia, Maryland). EG, DEG, and TEG were first separated with an ACE 3 C18-300 (100 \times 2.1 mm) column (Mac-Mod Analytical, Chadds Ford, Pennsylvania) with a gradient elution as follows: mobile phase A = HPLC water with 5% acetonitrile and 0.1% acetic acid, and mobile phase B = acetonitrile with 5% HPLC water and 0.1% acetic acid; using the following conditions, mobile phase B was held at 30% for 1 minute, linearly ramped to 95% over 4 minutes, held at 95% for 2 minutes, then re-equilibrated at 30% for 3 minutes. The column was heated at 40°C with a flow rate of 0.3 mL/min. The mass spectrometry variables are as follows: the samples were ionized with positive-mode electrospray ionization (ESI), curtain voltage (CUR) = 10, collision gas (CAD) = Med, ion source voltage (IS) = 5500, temperature = 300. Multiple reaction monitoring ion pairs were detected as indicated in the **Table** (available at www.jpeds.com), with the pair used for quantification in bold. Data were analyzed with Analyst software (Sciex). Limits of detection were 15 ng/mL for EG and DEG and 2 ng/mL for TEG.

Statistical Analyses

Comparisons between the concentrations of EG, DEG, and TEG in control plasma samples and plasma baseline values for the treatment group were performed with a Wilcoxon rank-sum test, with $P < .05$ as significant. Changes in EG, DEG, and TEG concentrations over time post-treatment were analyzed via a nonparametric repeated-measures ANOVA (Friedman) followed by Dunn multiple comparisons post hoc comparing each treatment with the baseline measure.

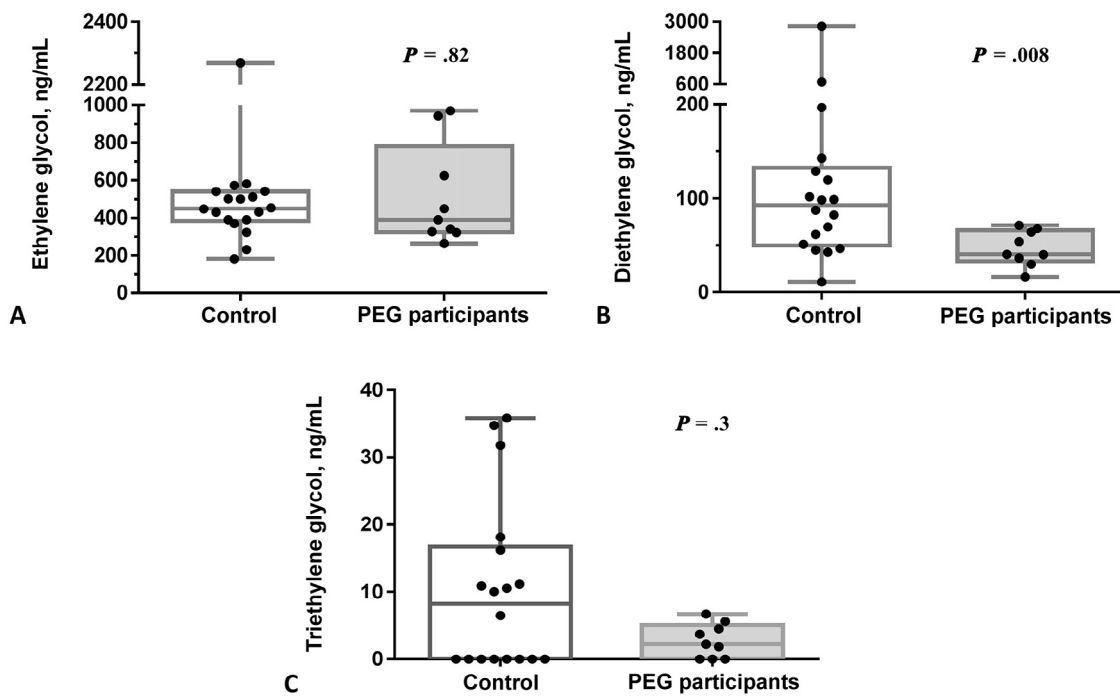


Figure 1. Baseline median and total ranges of blood levels of **A**, EG; **B**, DEG; and **C**, TEG of controls and study participants.

Results

Nine patients (4 males, 6.4–11.7 years old) taking PEG 3350 for constipation and 18 age- and sex-matched controls (8 males, 6.1–11.5 years old) were enrolled. Detectable levels of EG and DEG were present in all blood samples obtained from controls and from participants before their usual morning dose (Figure 1, A and B). Detectable TEG levels were found in the majority of blood samples tested (Figure 1, C). Baseline levels (median [IQR]) of EG (390.51 ng/mL [326.06, 624.55]) and TEG (2.21 ng/mL [0, 4.5]) in the 9 children on chronic PEG therapy did not differ from levels of EG (450.50 ng/mL [389.47, 540.69], $P = .82$) and TEG (8.26 ng/mL [0, 16.22], $P = .30$) in the control group. Baseline DEG levels were lower in children receiving PEG 3350 than in controls (40.13 ng/mL [36.69, 63.94] vs 92.83 ng/mL [51.06, 128.93], $P = .008$).

EG and TEG blood levels (median [IQR]) increased after ingestion of PEG 3350. Median EG levels (Figure 2, A) peaked at 90 minutes (1032.8 ng/mL [826.84, 1486.13], $P = .009$ vs baseline), and remained elevated at 180 minutes (921.17 ng/mL [872.43, 1100.63], $P = .04$ vs baseline). Median TEG levels (Figure 2) were significantly greater than baseline at 90 minutes (35.17 ng/mL [15.81, 45.13] vs baseline, $P = .0005$) and remained elevated through 150 minutes (31.79 ng/mL [13.56, 49.14] vs baseline, $P = .02$). Unlike median EG levels, TEG levels were not significantly different at 180 minutes (26.9 ng/mL [8.68, 39.49] vs baseline, $P = .29$). Blood levels of DEG did not significantly differ from baseline at any time point ($P = .99$ for all time points) (Figure 2, B).

Of note, the greatest levels of EG (1608 ng/mL) and DEG (155.9 ng/mL) measured after ingestion of PEG 3350 were lower than the greatest levels of EG (2269 ng/mL) and DEG (2828 ng/mL) measured in control samples. The greatest level of TEG (69.99 ng/mL) measured in the blood after ingestion of PEG 3350 was greater than greatest level of TEG (34.7 ng/mL) in control samples.

Detectable quantities of EG, DEG, and TEG were found in all 9 of the PEG 3350 laxative preparations provided by the study participants. The amounts per gram of PEG 3350 ranged between 13.9 and 23.3 μg of EG, 1.8 and 2.9 μg of DEG, and 1.3 and 1.8 μg of TEG. The average percentage of total weight of PEG 3350 samples was 0.00184% EG, 0.00025% DEG, and 0.00016% TEG. Based on these results, a standard 17-g dose of PEG 3350 in 8 oz (237 mL) of water would have resulted in concentrations (mean \pm SD) of EG, DEG, and TEG of $1.32 \pm 0.23 \mu\text{g/mL}$, $0.18 \pm 0.03 \mu\text{g/mL}$, and $0.12 \pm 0.01 \mu\text{g/mL}$, respectively (Figure 3).

Detectable levels of EG, DEG, and TEG were found in all weekly water samples taken weekly over 4 weeks. Mean EG, DEG, and TEG levels in tap water were 0.07 $\mu\text{g/mL}$, 0.21 $\mu\text{g/mL}$, and 0.02 $\mu\text{g/mL}$, respectively (Figure 4).

Discussion

Although EG, DEG, and TEG were found in PEG 3350, only the average EG and TEG blood levels increased after participants took their daily laxative dose. Finding EG, DEG, and TEG in the blood of control participants indicates all children are

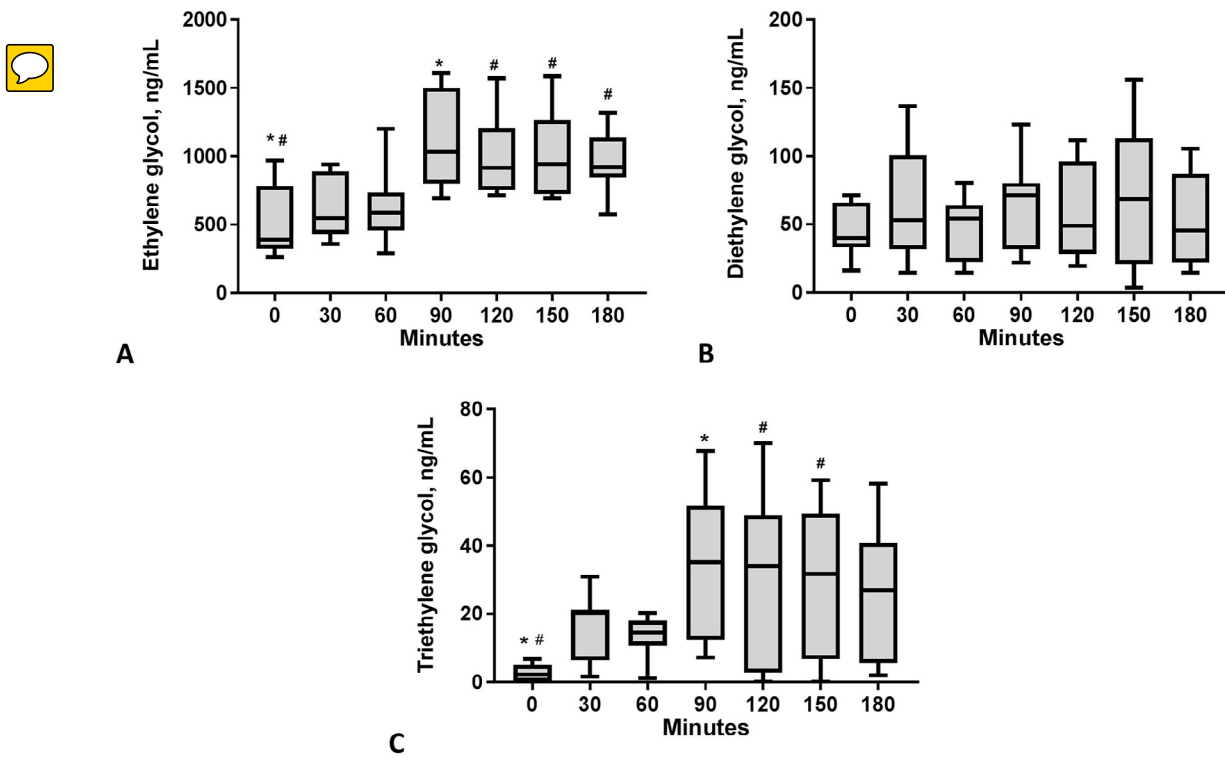


Figure 2. Median and total ranges of blood levels of **A**, EG; **B**, DEG; and **C**, TEG after ingestions of 17 grams of PEG 3350 (**P* < .01, #*P* < .05).

exposed routinely and have measurable amounts in the blood. The results from this preliminary study indicate that chronic use of PEG 3350 does not result in a sustained elevation of these compounds in the blood that is different from control children not on the laxative.

Analysis of water samples indicates that the increase in EG and TEG in blood is due to the EG and TEG in PEG 3350. The public water supply contains greater levels of DEG than EG and TEG. As DEG did not increase after dosing with PEG 3350, it is improbable that the EG and TEG in the water caused the increase in average blood levels of EG and TEG. The EG and

TEG found in PEG 3350 most likely caused the increases in EG and TEG. However, these increases were short lived, as there was no difference in baseline levels between those who took daily doses of PEG 3350 and those who have never taken PEG 3350.

Studies in animals indicate that very large doses of TEG are needed to cause toxic side effects. Chronic daily consumption of approximately 4000 mg/kg of TEG by rats for 90 days does not result in local or systemic specific organ or tissue toxicity.²² The samples analyzed in the current study would have contained approximately 22.1-30.6 μg of TEG per standard 17-g

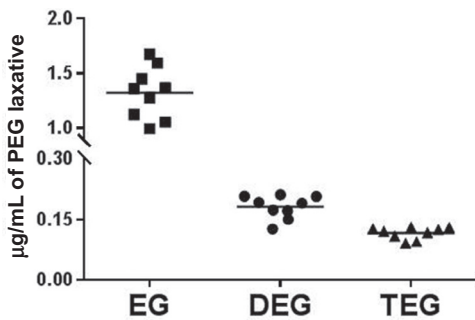


Figure 3. Calculated amounts of EG, DEG, and TEG in PEG 3350 suspended in 8 oz (237 mL) of water. Bar indicates mean.

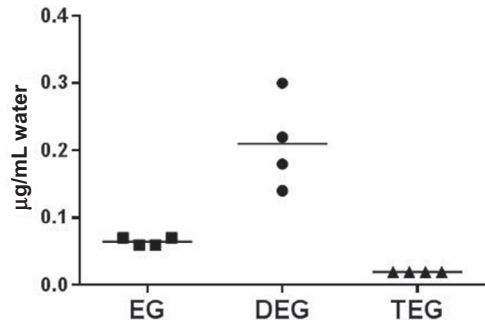


Figure 4. Amounts of EG, DEG, and TEG found in public water supply. Bar indicates mean.

dose of PEG 3350. It is unlikely that the level of TEG detected in the PEG 3350 samples would result in toxic side effects in animals or humans.

Although considered to be safe to humans at low levels, EG poisoning and toxicity to humans is common.²³⁻²⁵ In 2015, 5666 cases of EG exposures occurred in the US, with 1090 occurring in children younger than the age of 19 years of age.²⁶ Poisonings in children are generally accidental, and children often drink large amounts because EG has a sweet taste.²⁷ EG is found in large quantities in antifreeze, deicing agents, motor oil, photograph developing solutions, solvents, and paints.²⁷ Because of the high risks for EG toxicity and poisonings, several US governmental agencies are involved in setting guidelines and regulations for limiting exposure to EG.

The FDA allows the use of PEG compounds with mean molecular weights of 200-9500 to be added to food and pharmaceuticals for human consumption. Regulations limit the amount of EG and DEG that could potentially come from organic compounds that are used to create various products such as cosmetics, food additives, emulsifiers, adjuvants in nonnutritive sweeteners, and fillers in medications.²⁸ In fact, the FDA requires the total weight of any PEG additive not contain EG and DEG greater than 0.2%. The average EG and DEG content of the PEG samples in this study were a 100 and 800 times less, respectively, than this required 0.2% cutoff. Consequently, it is plausible that the PEG compounds approved for human consumption are the primary source for the baseline levels of EG and DEG that were detected in all our study participants.

Although the amounts of EG and DEG are well below the 0.2% cutoff, one must consider the potential health risk from the absolute amount of these compounds that are ingested from routinely prescribed daily doses of PEG 3350. The Agency of Toxic Substances and Disease Registry (ATSDR), a federal public health agency within the US Department of Health and Human Services, has published and routinely updates a toxicology profile for EG.²⁹ The ATSDR produces toxicology profiles for hazardous substances that are most commonly found at facilities on the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency. An ATSDR toxicology profile succinctly characterizes the toxicologic and adverse health effects information for various hazardous substances, such as EG. Each profile is peer-reviewed and includes key literature that describes a hazardous substance's toxicological properties.²⁹

Based on published reports, EG blood levels greater than 0.2 mg/mL are needed for acute toxic poisoning.³⁰ The average level of EG at the 90-minute peak of 1100 ± 350 ng/mL was 182 times lower than this level. The greatest level of EG found in any blood sample of this study was 88 times lower, and interestingly, this level was from a control participant not taking PEG 3350. Findings from the current study indicate that achieving EG levels needed for acute toxicity by ingesting PEG 3350 is highly unlikely.

Although risk for acute toxicity may be low, one must still consider the risk for adverse effects from prolonged exposure.

Estimates of exposure levels posing minimal risk level to humans have been made for EG by the ATSDR.²⁹ The ATSDR defines a minimal risk level as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. The toxicology profile for EG published by the ATSDR sets the minimal risk level to humans from oral consumption of EG for acute (14 days) and intermediate-duration (15-364 days) at 0.8 mg/kg/d.²⁹

The largest amount of EG per gram of PEG 3350 in this study was 23.3 μ g. The smallest participant in this study was a 6-year-old girl, who weighed 19.9 kg. For this participant to achieve 0.8 mg/kg/d from the sample with the greatest amount of EG, she would have had to ingest 683 g of the PEG 3350 sample per day. Translating into common clinical dosing terminology that equates 17 g as a capful of PEG 3350, she would have to take 40 capfuls of PEG 3350 per day for up to a year.

The ATSDR is not the only federal agency that has guidelines for daily exposure to EG. The Environmental Protection Agency publishes a table of Drinking Water Standards and Health Advisories that provides the concentration of various drinking water contaminants, including EG, that are considered to be safe for adults and children.³¹ The Environmental Protection Agency advises that children be exposed to no more than 20 mg/L EG in drinking water for 1 day, or 6 mg/L per day over 10 days. The advisories for children are based on what is considered safe for a 10-kg child who drinks 1 L of water per day. To achieve the limits of 20 mg or 6 mg of EG with the PEG 3350 sample with 23.3 μ g/g of EG, a 10-kg child would have to drink 1 L of water with 50 capfuls (858 g) in 1 day or 15 capfuls (258 g) per day for 10 days.

Although indicating that toxicity from EG, DEG, and TEG that occurs in PEG 3350 is highly unlikely in pediatric population, limitations of this study prevent affirming that PEG 3350 does not cause neuropsychiatric events. First, this study included only a small sample size of children taking PEG 3350. A small sample size precludes ability to speculate whether taking PEG 3350 is truly associated with lower DEG blood levels, as was found in this study. Furthermore, a small sample size may not have provided enough power to detect small differences in blood levels of EG and TEG. Studies with larger study populations are needed to confirm the findings of this study.

Second, neurotoxicity from EG and DEG is probably due to their metabolites.^{21,24} EG is metabolized to glycol aldehyde, glycolic acid, glyoxylic acid, and oxalic acid.²⁰ DEG is metabolized to hydroxyethoxyacetic acid and diglycolic acid.³² **Additional studies are needed to determine whether these toxic metabolites also are found in the blood of children who take PEG 3350.** Third, susceptibility to PEG 3350-related compounds may differ significantly in infants and the very young.³³ Finally, our study did not include children with known gastrointestinal mucosal disease that might compromise barrier function.

Although the current study finds that PEG 3350 contains trace amounts of EG, DEG, or TEG, the findings from this study indicate that these trace amounts did not result in a sustained elevation of these compounds in the blood of those

who take a standard oral dose of PEG 3350 on a daily basis. Although found to be in greater concentration than DEG and TEG, the levels of EG detected in PEG samples are far below established minimal levels believed to cause adverse side effects. The results from this study should help direct future investigations of the use of PEG 3350 in pediatric populations. ■

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Table. MRM precursor and product ions used in measurement of EG, DEG, and TEG

Analytes	Precursor ion [M + H] ⁺ , m/z	Product ion, m/z
EG	271.235	149.1
EG	271.235	104.9
DEG	315.232	105.2
DEG	315.232	149.0
TEG	359.249	149.1
TEG	359.249	105.1
Ethylene-d4-glycol	275.213	153.2
Ethylene-d4-glycol	275.213	105.1

MRM, multiple reaction monitoring.

Both ion pairs were used for identification, and bolded pairs were used for quantification.