Tolerable Exposure Derivation for Triethylene Glycol by Inhalation Route and Risk Assessment for Use of Grignard Pure, an antimicrobial air treatment product

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Product: Grignard Pure
Project No.: SC22067-GRI01

To Whom It May Concern:

Grignard Pure is an antimicrobial air treatment that reduces the level of hazardous pathogens in the air, where transmission is most likely. It, kills 99.9% of viruses and bacteria including the viruses that cause Cold, Flu and Covid; bacteria that cause hospital acquired infections including Pseudomonas, Klebsiella, MRSA, and TB; bacteria that cause food poisoning such as Salmonella and Listeria; and the microbes that are attributed to sick building syndrome.

Grignard Pure's novel approach to infection control utilizes only ingredients that are Generally Recognized as Safe (GRAS) by the Food & Drug Administration, without the use of more toxic chemicals such as chlorine or quaternary ammonium compounds (QACs). The technology forms an airborne barrier that goes right to work by denaturing the pathogen, destroying its ability to multiply, reducing virus and bacteria loads between an object or person and the source of the bacteria / virus.

Grignard Pure is dispersed into the air in small concentrations through an approved dispersion system. System settings are provided in the user manual for Controlled Time Release of the Grignard Pure by room size and can be monitored with a sensor or by the timing controls.

The product is intended to be used with technology that will result in repeated human inhalation exposure to the aerosolized product. Grignard Pure, LLC has retained Nelson Labs to perform a human health risk assessment of the chronic inhalation exposure to Grignard Pure, which contains triethylene glycol (TEG), the sole active ingredient in the product.

On January 15, 2021, Grignard Pure, LLC received approval from the EPA (U.S. Environmental Protection Agency) under its Section 18 Public Health Emergency Exemption program that will allow for the use of the technology solution in states that have requested its use..

Background and Purpose

Triethylene glycol (TEG) is a bacteriostatic (active ingredient) that comprises slightly more than 50% of the Grignard Pure product. The aerosolized product is expected to give rise to an airborne concentration of the product from 0.1 mg/m^3 to 1 mg/m^3 (with a maximum of 2 mg/m^3). The purpose of this scientific memo is to evaluate and derive an inhalation Tolerable Exposure (TE) limit for the

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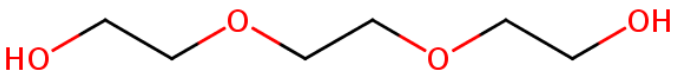
TEG in Grignard Pure that is expected to pose negligible toxicological risk to humans from evaluation of the current literature and to compare that level to exposure levels resulting from the intended use of the product.

Derivation of Tolerable Exposure for Triethylene Glycol



Triethylene Glycol (TEG)

Products containing TEG are used as a fungicide, virucide, and miticide for disinfection of hard, non-porous surfaces and as an insecticide (against lice) by direct application to caged birds and bird cages. It was first registered by the EPA as an air sanitizer on August 3, 1948 (James Varley & Sons' Glyco Mist, EPA Reg. No. 421-21). As an air sanitizer, it has numerous listed active use sites including household or domestic dwellings, automobiles, taxis, limousines, hospitals, commercial and industrial equipment, laundry equipment, bathroom premises, refuse and solid waste containers, and hard non-porous surface treatments.

TEG received 'Generally Regarded As Safe' status for use as a food additive by U.S. FDA. 21 CFR 175.300 lists TEG as an indirect food additive for human food consumption as a component in polyester resins for coatings not exceeding a coating weight of 4 milligrams per square inch. TEG is also listed as a US FDA approved drug excipient in Sustol a polymeric subcutaneous formulation of granisetron for the prevention of chemotherapy-induced nausea and vomiting. The primary component of the polymer is a triethylene glycol poly(ortho ester) polymer (TEG-POE at 80%) and a minor component (methoxy polyethylene glycol, MPEG, 20%). Additionally, in EPA's memorandum for TEG for its use as an antimicrobial (US EPA - Pesticides - Reregistration Eligibility Decision (RED) for Triethylene Glycol | US EPA ARCHIVE DOCUMENT[1]) the following were concluded regarding TEG;

- Based on a review of the available toxicology data, the Agency has concluded that TEG is of very low toxicity by the oral, dermal, and inhalation routes of exposure.
- The toxicology database is adequate to characterize the hazard of TEG, and no data gaps have been identified.
- There are no indications of special sensitivity of infants or children resulting from exposure to TEG.
- The Agency has not identified toxicological endpoints of concern for the active and the inert uses of TEG.
- The Agency has no risk concerns for TEG with respect to human exposure.

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- Ecological effects data were previously waived due to the use of TEG as an indoor microbiocide, its high volatility, and known low toxicity (it is a preferred solvent for aquatic organism toxicity tests).

- **Regulatory Decision:** The Agency has completed its review and has determined that the data are sufficient to support reregistration of all supported products containing TEG.

TEG exhibits complete and rapid absorption after oral administration with more than 90% of parent compound excreted in urine.[2,3] Metabolism of TEG is expected to be limited with majority of the compound found unchanged in urine, with some monocarboxylic acid arising by metabolic oxidation of the terminal hydroxyl group as well as glucuronide conjugation of the parent glycol, thus indicating low bioaccumulation potential.[2,4] It should be noted the metabolism decreases with increasing chain length of the ethylene oxide units.

The US EPA has derived a chronic provisional oral RfD for TEG of 2 mg/kg/day with the critical effect being delayed ossification of the supraoccipital bone in fetal mice. No inhalation RfC has been derived to date for TEG, however, several inhalation studies have been conducted to date.[5]

The inhalation exposure effects of TEG in animals have been evaluated in two short-term-duration studies, one subchronic-duration study, and three chronic-duration studies (further details located in Provisional Peer-Reviewed Toxicity Values for Triethylene Glycol (CASRN 112-27-6).[5] No inhalation studies for developmental, reproductive, or carcinogenic effects of TEG in animals were identified in the literature.

Rhesus macaque monkeys (n=17 monkeys) were exposed continuously by inhalation to approximately 4 mg/m3 supersaturated TEG vapor in air from one to 10 months, and 8 monkeys were kept in a separate chamber containing normal air from 5 to 8 months. Decreased body weight, browning of the skin of the face, and crusting of the ears in exposed monkeys occurred. Hematology, blood chemistry, and urinalysis were similar between the TEG exposed and control animals. In a separate study, eight rhesus macaque monkeys were exposed continuously by inhalation to approximately 2–3 mg/m^3 TEG vapor from 2 weeks to 10 months, and eight monkeys were kept in a separate chamber containing normal air for the same length of time. No adverse reactions or histopathological changes were noted. Accordingly, a NOAEL of 3 mg/m^3 was identified.

Other inhalation studies for other structurally similar glycols, such as PG or dipropylene glycol (DPG) with similar intended use as air sanitizers, were concluded by the US EPA Office of Pesticides Program that inhalation poses no toxicological concerns when used according to pesticide labeled uses, as no significant toxicity was observed in any of the animal toxicity studies (RED 2006).[6]

The inhalational toxicity data for PG was further reviewed to determine if a read across approach using PG could help to assess potential inhalational toxicity of TEG. Only two studies were available and both suggest lack of potential inhalational toxicity for PG. Based on the nasal irritation observed from a 90-day subchronic nose-only inhalation toxicity study in which rats were exposed to increasing concentrations of aerosolized PG, the ATSDR established an intermediate duration (15-364 days) MRL value of 0.009 ppm (28 µg/m^3).[7] However, US EPA considered these effects not clinically relevant and dose-independent to establish a RfC value. The European Medicines Agency has established a lowest threshold exposure of 1

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mg/kg/day for PG from medicinal products used in neonates from all intended routes of administration, including inhalation (EMA/CHMP/704195/2013).

U.S. EPA has completed its assessment of the dietary, drinking water, residential, ecological and occupational risks associated with the use of pesticide products containing the active ingredients PG and DPG (EPA-739-R-06-002, 2006). Based on its review, the Agency determined that the toxicological data are sufficient to support reregistration of all supported products containing PG and DPG, as no toxicological endpoints were identified, similar to the assessment of TEG as discussed above.

It should be noted that EPA granted an exemption from the requirement of tolerance for residues of antimicrobial pesticide ingredients for DPG, TEG (78 FR 48618), and PG (78 FR 48618) when used or applied to food contact surfaces in public places including processing equipment. Since, EPA concluded that for registration review, these chemicals pose no toxicological concerns when used according to pesticide labeled uses as no significant toxicity was observed in any of the animal toxicity studies in the existing toxicological database for registration review, and given the toxicological similarities between these glycols, TEG and PG aggregate exposure may not be of toxicological concern.

Due to the above referenced information, the high oral bioavailability of TEG, the provisional RfD of 2 mg/kg/day will be used to derive the Tolerable Intake (in mg/kg/day) and TE (in µg/day). The Uncertainty Factors (UF) considered were: UF1 and UF2 assigned a value of 1 each as the provisional oral RfD already accounts for potential inter-individual differences and uncertainty with respect to animal-to-human toxicity extrapolation. A value of 2 was used since oral absorption is high and to account for potential toxicological differences in inhalation exposure. Therefore, TI is calculated as follows:

$$TI = \frac{RfD}{(UF1 \times UF2 \times UF3)}$$

$$\mathrm{TI} = \frac{(2\ \mathrm{mg/kg/day})}{(1 \times 1 \times 2)}$$

$$\mathrm{TI} = 1\ \mathrm{mg/kg/day}$$

The TE is therefore calculated as follows:

$$\mathrm{TE} = \mathrm{TI} \times \mathrm{m_B}$$

$$\mathrm{TE} = (1\ \mathrm{mg/kg/day}) \times (70\ \mathrm{kg}) = 70\ \frac{\mathrm{mg}}{\mathrm{day}}\ \text{or}\ 70{,}000\ \frac{\mu\mathrm{g}}{\mathrm{day}}$$

The TE value depends on the body weight of the exposed individual. Value of m_B chosen for the calculation above was the adult male body weight according to ISO 10993-17 default recommendations. (Additional ISO 10993 body weights for other age groups are shown in **Table 2** below). Exposure can be derived for each population group by considering the maximum (worst-case) exposure to TEG from the use of the aerosolized Grignard Pure product of 2 mg/m^3 and the ISO 18562 default breathing rates for adults (20 m^3/day), pediatrics (5 m^3/day), infants (2 m^3/day), and neonates (0.2 m^3/day). Since TEG comprised of

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~50% of the product, 1 mg/m^3 TEG concentration will be assumed for determining exposure. A summary of these exposures is provided in **Table 1**.

Table 1. Exposure in Each Population

Target Population	Inhalation Rate (m^3/day)	Worst Case Exposure Concentration of TEG (mg/m^3)	Worst Case Exposure Amount* (µg/day)
Adults	20	1	20,000
Pediatrics	5		5,000
Infant	2		2,000
Neonate	0.2		200

**Assumes exposure occurs continuously for 24 hours a day*

An example of the Margin of Safety for the adult male and the worst-case concentration exposure to Grignard Pure can be calculated as follows:

$$\text{Margin of Safety} = \frac{\text{TE}}{\text{Exposure}} = \frac{\left(70{,}000\,\frac{\mu g}{\text{day}}\right)}{\left(20{,}000\,\frac{\mu g}{\text{day}}\right)} = 3.5$$

A summary of the MOS for the target populations is shown below.

Table 2. Margin of Safety Summary for Triethylene Glycol

Target Population	Weight (kg)	TE (µg/ day)	Worst Case Exposure Amount (µg/day)	Margin of Safety
Adult Male	70	70,000	20,000	3.5
Adult Female	58	58,000		2.9
Pediatrics	10	10,000	5,000	2.0
Infants*	9.2	9,200	2,000	4.6
Neonate	3.5	3,500	200	18

**Infant body weight is not specified per ISO 10993, therefore 9.2 kg (mean body weight for a 6-11 month-old per EPA exposures handbook) was used*
a) A MOS greater than a value of 1 is indicative of low toxicological hazard

Several conservative approaches were used in the calculations of the MOS values: 1) the total amount of TEG exposure was based on the worst-case concentrations of Grignard Product used and assumed exposure or 24 hours every day, 2) UF3 was raised to account toxicological uncertainties in the different route of exposure. The calculated MOS values above support a low toxicological hazard associated with the TEG exposure from aerosolized use of the Grignard product.

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Conclusion

Using the currently available toxicological literature on TEG to derive a TE results in favorable MOS values and indicate that the likelihood of adverse effects from continuous inhalation exposure to TEG resulting from the aerosolized use of the Grignard Pure product is considered low. This assessment also indicates that acute, subacute/subchronic, and chronic toxicity, genotoxicity, and carcinogenicity from the exposure to TEG from the intended use of the product are not expected. Additional animal testing is not justified and would not follow the guidance regarding animal welfare.

Scientific Memo completed by:

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