# Assessing the Safety of Grignard Pure

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    Clinical Professor, NYU School of Global Public Health
- Pure Earth / Blacksmith Institute; 2006 - present
  - Director of Research / Science Advisor
- Global Alliance for Health & Pollution, USA (NY, NY); 2012 - present
  - Senior Technical Advisor
- Board Certified in Industrial Hygiene (CIH); 1990 - present
  - American Board of Industrial Hygiene
- Authorized OSHA Construction Industry Health & Safety Trainer

# William Jordan

- 40 Years at US Environmental Protection Agency (ret. 2016)
  - Deputy Director of EPA Office of Pesticide Programs
    - Extensive collaboration with EPA scientists on regulatory policies, assessments, & decisions
    - Responsible for EPA science policies for pesticide regulation
- Currently, independent environmental consultant
  - Volunteer work:
    - Pesticide team lead for Environmental Protection Network,
    - Farmworker Justice,
    - Equitable Food Initiative, EarthJustice, and other NGOs
  - Compensated work:
    - With pesticide companies and regulatory services companies to help bring safer products to market

# Safety of Grignard Pure

1. Government agencies (EPA, FDA) have judged the active ingredient in Grignard Pure, Triethylene Glycol [TEG], to be “low risk” when used in products regulated by the agencies.

2. Exposure to TEG from use of Grignard Pure would be below recommended safe exposure limits and hundreds of times lower than the concentration that caused no systemic effects in inhalation toxicity studies with laboratory animals.

3. Exposure to TEG aerosol may cause transient, mild irritation of eyes, nose, or throat in some sensitive individuals

# Introduction

# What is Grignard Pure?

- Grignard Pure represents a new type of antimicrobial product with an innovative, low risk, airborne viricidal technology that will help to combat the spread of the SARS-CoV-2 virus that causes the COVID-19 disease.

- It works to reduce the number of viral particles in indoor locations, where the risk of transmitting the COVID-19 virus is greatest – in the air.

- A constant concentration of microdroplets of Grignard Pure is produced in indoor spaces, while people are present, and starts to kill airborne virus particles as they are released by infected individuals.

# Other Uses of the Active Ingredient (AI)

- The Active Ingredient (AI) in Grignard Pure is Triethylene Glycol (TEG); TEG has uses other than as an antimicrobial air treatment, including:
  - Air sanitizers regulated by US EPA
  - “Indirect” food additives regulated by US FDA
  - Atmospheric haze products used by the film, theater, TV, and entertainment industries
- Government agencies, in particular EPA’s Pesticide Office as well as independent third parties, have assessed the safety of TEG


# INDOOR VENUES

# ENTERTAINMENT EVENTS

# INDOOR COMMON AREAS

# RESTAURANT DINING

# Assessing the Safety of Triethylene Glycol

# Outline of Safety Presentation (1)

- Overview of EPA regulation of pesticides & risk assessment concepts
- Characterizing the Inhalation Hazard of TEG
  - Adequacy of available animal toxicity information for TEG
  - Laboratory animal studies of chronic inhalation toxicity of TEG
  - Reports on Human Experience with TEG-based Products
  - EPA's Overall Characterization of TEG's Risks to Humans and the Environment

# Outline of Safety Presentation (2)

- Evaluating Inhalation Exposure to TEG
- Government & Independent Safety Assessments
- Preliminary Inhalation Risk Assessment for Use of Grignard Pure
- Conclusions

# Overview of EPA Regulation of Pesticides & Risk Assessment Concepts

# Outline of Safety Presentation (1)

- **Overview of EPA regulation of pesticides & risk assessment concepts**
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# EPA Regulation of Pesticides (1)

- The term, “pesticide,” covers a wide variety of products, including antimicrobial products that kill bacteria, viruses, and other microbes

- The active ingredient in Grignard Pure – Triethylene Glycol – is both an active and inert ingredient in EPA-registered pesticides; many of these EPA-registered pesticides are applied as aerosols

- It is illegal to sell a pesticide product unless EPA has first approved the formula, labeling, and packaging of the product – “registration”

# EPA Regulation of Pesticides (2)

- EPA requires the registrant to prove use of a pesticide will be “safe” by providing studies of:
  - Effects on people who mix, load or apply the pesticide and who could be exposed to the pesticide through food, water, or other pathways
  - Effects on the environment, and
  - In the case of antimicrobial pesticides making public health claims, product efficacy
- EPA is required to reevaluate and update its registration decisions periodically
- EPA publishes documents summarizing their safety assessments
- Consequently, there is a lot of excellent, current, scientific analysis of the safety of exposure to TEG in aerosols

# Risk Assessment Concepts

- “Risk” is a description of the likelihood that something adverse will happen.
- For chemicals, risk depends on both “hazard” and “exposure”
  - Many everyday substances – aspirin and salt, for example – do not cause harm in small amounts, but can be fatal in large enough doses
  - Conversely, some substances are lethal in minute quantities.
  - Exposures vary in many ways – route, duration, level – and from individual to individual
- A meaningful risk assessment compares the hazard – the amount that is harmful – with expected exposure

# Science of Assessing the Risk of a Chemical Exposure

The approach for quantitative risk assessment of chemicals (modeled on National Academy of Sciences / EPA) has three steps:

1. Determine the "Point of Departure" [POD] (the level of exposure in toxicity studies that will not cause adverse effects)
2. Select appropriate Safety or Uncertainty Factors [UFs] and divide the POD by the UFs to determine a recommended safe level of exposure
3. Compare the recommended safe level of exposure to estimated / measured level of exposure

- If exposure > recommended safe level = PROBLEM
- If exposure < recommended safe level = NO REASON FOR CONCERN

# Types of Toxicity Data

Broadly speaking, there are two types of toxicity information about a chemical; a well-studied chemical will have a full dataset of both types

- Animal data – laboratory testing in which scientists compare the effects of a chemical on animals exposed to the chemical with unexposed animals
  - Different types of effects
  - Different routes of exposure
  - Different exposure durations
- Human Experience
  - Epidemiological studies
  - Incidents & case reports

# Sources of Exposure Data and Estimates

Evaluating potential exposure is the second essential component of a risk assessment; there are several ways to evaluate exposure

- Exposure limits established by a regulatory authority
- Exposure measurements taken under real world conditions
- Laboratory measurements that simulate real world conditions
- Exposure estimates based on models that predict real world conditions

# Adequacy of the Available Animal Toxicity Information for TEG

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# EPA Reregistration Eligibility Decision for TEG

- Based on a review of the available toxicology data, the Agency has concluded that triethylene glycol is of very low toxicity by the oral, dermal, and inhalation routes of exposure. The toxicology database is adequate to characterize the hazard of triethylene glycol, and no data gaps have been identified.

- The Agency has not identified toxicological endpoints of concern for the active and the inert uses of triethylene glycol. The Agency has no risk concerns for triethylene glycol with respect to human exposure.

Source: 2003 EPA Reregistration Eligibility Decision [RED] for TEG https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-083501_26-Sep-03.pdf [p. 1]

# Adequacy of Toxicity Data for TEG: Animal Studies

- The toxicological database for triethylene glycol is currently comprised of published and unpublished studies either submitted to the Agency or obtained directly from the open literature. Although the available studies do not meet the requirements of the Agency's OPPTS harmonized test guidelines published in 1998, it was determined that these studies contain useful information that is adequate for hazard characterization of triethylene glycol. These acceptable non-guideline studies include acute, sub-chronic, chronic, developmental, and reproductive toxicity, carcinogenicity, mutagenicity, metabolism / pharmacokinetics and dermal absorption studies. Therefore, the Agency has determined that the toxicological database is complete and sufficient [.]"

Source: 2003 EPA Reregistration Eligibility Decision [RED] for TEG https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-083501_26-Sep-03.pdf [p. 8]

# Adequacy of Toxicity Data for TEG – EPA, 2013

## Animal Studies

- During its 2013 reevaluation of TEG and two other glycols, EPA reached the same conclusion that the toxicity database for these chemicals was complete.
  - Source, EPA Registration Review document: Propylene Glycol, Dipropylene Glycol, and Triethylene Glycol Preliminary Work Plan (2013), available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0219-0002

# Adequacy of Toxicity Database – NIH, 2020

- The PubChem database maintained by the National Institutes of Health [NIH] is a public, online compilation of references and summaries of scientific studies and assessments of chemicals by government agencies and independent scientists.
- The PubChem files for TEG is available at: https://pubchem.ncbi.nlm.nih.gov/compound/8172 , and lists over 75 citations to studies of the toxicity and metabolism of TEG

# Laboratory Animal Studies of Chronic Inhalation Toxicity of TEG

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# Ballantyne, et al., (2006)

**Whole Body Aerosol Exposure Study with Rats**

- Animals exposed 6 hours / day for 9 days over two weeks
- Concentrations were 94, 2011, or 4842 mg/m$^3$
- Mild clinical signs – “swollen periocular tissues and perinasal encrustations” – observed at middle and low dose levels; organ weight and blood chemistry changes also observed

**Nose-Only Aerosol Exposure Study with Rats**

- Animals exposed 6 hours / day for 9 days over two weeks
- Concentrations were 102, 517, or 1036 mg/m$^3$
- No treatment-related toxicities were seen at any dose tested

Ballantyne B, Snellings WM and Norris JC (2006). Respiratory peripheral chemosensory irritation, acute and repeated exposure toxicity studies with aerosols of triethylene glycol. J. Appl. Toxicol. 26: 387-396.

# Robertson, et al., (1947)

**13 Month, Whole Body Vapor Exposure Study with Rats**

- Exposed to a "fog" (3.1 – 4.6 mg/m$^3$) of TEG vapor 24 hrs./day
- No differences between treated and control rats in blood or autopsy measurements; treated group experienced greater weight gain

**13 Month, Whole Body Vapor Exposure Study with Monkeys**

- Exposed to a "fog" (3.1 – 4.6 mg/m$^3$) of TEG vapor 24 hrs./day
- Apart from a "browning" of treated monkeys' facial skin (possibly due to an ectoparasite infestation) and less weight gain, treated and control animals were "essentially the same"

**10 Month, Whole Body Vapor Exposure Study with Monkeys**

- Exposed to "fog-free" (2 – 3 mg/m$^3$) TEG vapor 24 hrs./day
- No browning of facial skin, but more rapid weight gain in treated group; also cellular changes in lung indicating possible chronic irritation

Robertson, O. H., C. G. Loosli, T. T. Puck, H. Wise, H. M. Lemon, and W. Lester, Jr. 1947. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *J. Pharmacol. Exp. Ther*. 91:52–76.

# Summary of Inhalation Toxicity Studies in Animals

5 intermediate and long-term inhalation toxicity studies

- Some results suggest TEG may cause irritation:
  - Indication of irritation effects in eyes and nose at levels in Ballantyne whole body aerosol study,
  - In Robertson vapor study, some cellular changes in monkeys' lungs exposed to 2 – 3 mg/m$^3$,
- Other studies by the same researchers indicate exposure does not cause systemic adverse effects:
  - In Ballantyne nose-only rat study at up to 1036 mg/m$^3$
  - In Robertson vapor studies, no indication of systemic effects in rats at 4 mg/m$^3$ or in monkeys at 3 – 4 mg/m$^3$

# Reports on Human Experience with TEG-based Products

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# Health Hazard Evaluation Report – NIOSH 1991, 1993

National Institute of Occupational Safety and Health (NIOSH) investigated the possible effects associated with the use of theatrical "smoke" in Broadway productions.

- 224 Broadway actors (134 exposed to "theatrical smoke;" 90 not). Compared symptoms in exposed and unexposed actors.

- "Smoke" from multiple glycols – Triethylene Glycol, Propylene Glycol, Ethylene Glycol, Butylene Glycol and Diethylene Glycol.

Burr, G. A., et al. "Health Hazard Evaluation Report" (1991, 1993). https://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0355-2449.pdf

# Health Hazard Evaluation Report – NIOSH 1991, 1993 (2)

- Based on results of this study, there is no evidence theatrical 'smoke', at the levels found in the theaters studied, is a cause of occupational asthma among performers.
- Analysis of bulk samples detected Triethylene glycol levels at < 0.04 to 3.7mg/$m^3$ (0.006ppm – 0.6ppm).
- Triethylene Glycol acute and chronic oral toxicity is very low. Has not been shown to be a significant skin or eye irritant. Unlikely that significant amounts of this compound could be absorbed through skin.

Burr, G. A., et al. "Health Hazard Evaluation Report" (1991, 1993). https://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0355-2449.pdf

# Moline Study of Health Effects

## Theatrical Smoke, Haze and Pyrotechnics

- The goal of this epidemiological study was to determine whether associations exist between exposure to theatrical effects (i.e. smoke, haze and pyrotechnics) and health effects, taking into account the specific work environment and activities involved in a professional theatrical musical production.
- An epidemiological and exposure assessment of 439 adult Broadway actors for "local irritant effects of the respiratory tract and eyes" was conducted.
- Like NIOSH, studied mineral oil and multiple "glycols;" toxicity profiles of other substances indicated greater toxicity than TEG.

Source: "Health Effects Evaluation of Theatrical Smoke, Haze, and Pyrotechnics," Moline, J. M. et al. (Mt. Sinai School of Medicine & ENVIRON, 1999) (sponsored by Actors Equity Assoc.) https://www.actorsequity.org/resources/producers/safe-and-sanitary/smoke-and-haze/finalreport.pdf p. ES-1,2,3

# Human Experience –Moline, et al. Study (2)

"No significant acute change in voice quality, pulmonary function, or vocal cord appearance was found among Actors exposed to theatrical smoke, haze, or pyrotechnic agents. However, Actors with exposures to elevated or peak levels of glycols reported more symptoms than Actors with less exposure. In addition, some mild chronic effects in Actors with greater exposure to peak levels of glycols and mineral oil were observed. These findings may reflect a negative health impact of exposure to theatrical agents or other factors (e.g., physical demand)."

P. ES-3 9 (emphasis added)

# Bigg, et al. (1945)

- Field trial conducted in dormitories of a military camp where rotating groups totaling ~ 2000 men were housed over the course of the study – half in ”treatment” groups and half in “control” groups.
- Soldiers in the treatment groups were exposed to 2.5 – 3 mg/$m^3$ of TEG vapor at night for six weeks.
- Primary purpose was to measure levels of airborne bacteria and incidence of bacterial infections in treatment vs. control groups.
- Study also reported “Frequent interrogation of the men concerning possible effects of the vapor elicited no evidence of irritation of the respiratory tract.”

Bigg E., Jennings B. H. and Olson F. C. W. (1945). Epidemiologic observations on the use of glycol vapors for air sterilization. Am J Public Health 35: 788-798

# Observations from Special Effects Professionals

As noted earlier, TEG-based fluids are used to simulate fog and smoke and to produce lighting effects for the TV and film industries. Several professionals from the Alliance of Special Effects and Pyrotechnic Operators [ASEPO], who are responsible for managing these products, described their experiences with TEG fluids over decades of use. James Streett, ASEPO president, observed:

- '[W]e are often exposed to fog daily (10-14 hrs) for months at a time."
- "Although people can temporarily experience a dry mouth or eyes in cases of extreme exposures, easily relieved with some water or fresh air, we have never seen or been made aware of any chronic reactions."

Chernick, J. (2020). Letter concerning the impacts of chronic exposure to lighting effects products on health and safety of theatrical workers.

Krauss, Justin (2020). Letter concerning the impacts of chronic exposure to lighting effects products on health and safety of film production workers.

Streett, J., et al. (2020) ASEPO letter concerning the impacts of chronic exposure to lighting effects products on health and safety of theatrical workers.

All letters available on request from Grignard Pure, LLC.

# Incident Reports for TEG Pesticides

After reviewing multiple organizations that collect reports on poisoning incidents, EPA's Pesticide Office concluded:

> "Although there are incidences [sic] that have been reported associated with TEG in the searched database, there is no one reported incident involving TEG as a single chemical exposure. Either no effects or minor effects are involved in these reported incidences [sic]. The other ingredients in combination with TEG may be the reasons for the symptoms that have been reported."

- Source: https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-083501_26-Sep-03.pdf [p. 10]

# Summary of Human Experience with TEG

There is consistency across the various types of information – observations during an efficacy trial with soldiers, two occupational safety studies, industry professionals' observations, and a survey of complaints in pesticide incident reports. They indicate:

- Exposure to TEG- based aerosols may cause small percentage of individuals, to have transient ocular and respiratory irritation, i. e., dry eyes, nose, and throat.
- Complaints seem to occur more often when levels are high enough to produce a smoke or fog effect, e.g., concentrations greater than 10 $mg/m^3$.
- Reported complaints of respiratory irritation may be explained by other factors, such as exposure to other chemicals or psychosomatic responses.
- Irritation is relatively mild and subsides with fresh air or water.
- No information about the human experience suggests chronic inhalation exposure to TEG causes systemic effects.

# EPA's Overall Characterization of TEG's Risks to Humans and the Environment

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# TEG has “no endpoints of concern” – EPA, 2003

Upon reviewing the available toxicity information, the Agency has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to triethylene glycol. This conclusion is based on the results of toxicity testing of triethylene glycol in which dose levels near or above testing limits . . . were employed in experimental animal studies and no significant toxicity observed.”

- Acute Eye Irritation of concentrated TEG – mild, quickly reversible eye irritation
- Acute Inhalation Toxicity – LC 50 greater than 5.2 mg/L = 5200 mg/m$^3$ – RED, p. 8;

Source: EPA Memorandum “***TRIETHYLENE GLYCOL:*** Revised Antimicrobials Division’s Review of the Disciplinary Sciences for Issuance of the Reregistration Eligibility Decision (RED) Document.” available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2005-0250-0002

# TEG is "Without Adverse Toxic Effects" – EPA, 2003

"Repeat dose toxicity studies by the oral, dermal, and inhalation routes at doses near or above the limit doses for such studies (1000 mg/kg/day for oral and dermal studies, 1000 mg/m$^3$ for inhalation studies) have also shown a lack of systemic toxicity or toxicity only at doses in excess of the limit dose. . . . Chronic exposure of experimental animals to triethylene glycol at doses equivalent to or in excess of the limit dose for such studies has shown the chemical to be without adverse toxic effects. [pp. 6 – 7]

Source: EPA Memorandum "***TRIETHYLENE GLYCOL:*** Revised Antimicrobials Division's Review of the Disciplinary Sciences for Issuance of the Reregistration Eligibility Decision (RED) Document." available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2005-0250-0002

# TEG is “negative for carcinogenicity” – EPA, 2003

- A review of the available data has shown triethylene glycol to be negative for carcinogenicity in studies conducted up to the testing limit doses established by the Agency; therefore, no carcinogenic analysis is required.”
- Triethylene glycol was tested for mutagenic or genotoxic potential and found to be negative in a battery of studies…”

Source: 2003 EPA Reregistration Eligibility Decision [RED] for TEG https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-083501_26-Sep-03.pdf [p. 9]

# TEG is not more risky for infants or children – EPA, 2003

- There are no indications of special sensitivity of infants or children resulting from exposure to triethylene glycol.
- The Agency has concluded that the FQPA Safety Factor for triethylene glycol should be removed (equivalent to 1X) because there is no pre- or post-natal evidence of increased susceptibility for infants and children following exposure to triethylene glycol.

Source: 2003 EPA Reregistration Eligibility Decision [RED] for TEG https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-083501_26-Sep-03.pdf [p.2 & 3]

# TEG: “there is a reasonable certainty of no harm for infants and children” – EPA, 2003, 2019

- EPA has determined that the established exemption from a requirement for tolerance for triethylene glycol, meet the safety standards under the FQPA amendments to section 408(b)(2)(D) of the FFDCA, that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children considers factors of the toxicity, use practices, and environmental behavior noted above for the general population, but also takes into account the possibility of increased dietary exposure due to the specific consumption patterns of infants and children, as well as the possibility of increased susceptibility to the toxic effects of triethylene glycol residues in this population subgroup

Source: 2020 Dipropylene Glycol and Triethylene Glycol; Exemption From the Requirement of a Tolerance

# TEG is Safe to Use Around Food

## Exemption From the Requirement of a Pesticide Tolerance

- Although the current uses have the potential to result in exposure to residues of dipropylene and triethylene glycol in or on food, including uses of these chemicals as inert ingredients, the low order of toxicity and low application rates from the current uses of these chemicals support a conclusion that exemptions from the requirement of a tolerance for these pesticide chemicals when used in antimicrobial formulations on food-contact surfaces in public eating places, on dairy processing equipment, and on food processing equipment and utensils would be safe.
- Based on the low order of toxicity and low exposure levels, EPA concludes that there is a reasonable certainty that no harm will result to the U.S. population, including all subpopulation groups, from aggregate exposure to dipropylene glycol or triethylene glycol.

Source: https://www.govinfo.gov/content/pkg/FR-2020-05-22/pdf/2020-10805.pdf

# TEG: EPA “has no risk concerns for TEG with respect to non-target organisms” EPA, 2003

- The Agency has relied on open literature data that characterizes the fate properties of triethylene glycol. The results of these studies indicate that triethylene glycol is miscible in water, mobile in soils and stable to abiotic degradation hydrolysis and soil and aquatic photolysis. Biodegradation is expected to proceed rapidly in surface waters.
- Data obtained from published studies provide additional confirmation of the low toxicity of the compound to fish and aquatic invertebrates. The Agency has no risk concerns for triethylene glycol with respect to non-target organisms. The Agency expects no effects to listed species or critical habitat…”

Source: 2003 EPA Reregistration Eligibility Decision [RED] for TEG https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-083501_26-Sep-03.pdf [p.1]

# Summary of Inhalation Toxicity Information for TEG

There is consistency across the type of information available from animal testing and the human experience. Considering both animal toxicity studies and human experience reports:

- Chronic inhalation exposure to high levels of TEG (up to ~ 1000 $mg/m^3$) does not cause systemic adverse effects
- Inhalation exposure to TEG may cause mild, transient irritation of eyes, nose, and throat in sensitive individuals

# Evaluating Inhalation Exposure to TEG from use of Grignard Pure

# Outline of Safety Presentation (2)

- **Evaluating Inhalation Exposure to TEG from use of Grignard Pure**
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# EPA-approved label for Grignard Pure

# GRIGNARD PURE™

## Continuous Antimicrobial Air Treatment

Kills 98% of airborne SARS-CoV-2 virus when in use.
For indoor use only in both occupied and unoccupied spaces.

Follow SARS CoV-2 risk mitigation guidelines issued by Federal, State and local public health officials. Grignard Pure is not to be relied upon as a sole mitigation but is a supplemental treatment to be used in conjunction with current public health guidelines. See **Directions for Use** for specific details regarding criteria for use of this product.

**CAUTION:**
KEEP OUT OF REACH OF CHILDREN

Read the entire label before using. Follow all applicable directions, requirements, and precautions. Any adverse effects from the use under these exemptions must immediately be reported to the manufacturer: 1 (855) 642-PURE (7873).

**ACTIVE INGREDIENT**
**Triethylene Glycol……..52.25%**
**INERT INGREDIENTS…….47.75%**
**TOTAL……..100.00%**
**Patent Pending**
**Net Content 1 Gallon (3.78L)**

**DIRECTIONS FOR USE**

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

**Handling**: After handling, always wash hands thoroughly with soap. Wipe up spills immediately to avoid slips and falls.

Grignard Pure is designed to reduce the level of airborne SARS-CoV-2 virus, based on testing with a surrogate virus.

Grignard Pure is for use with only Grignard Pure-certified air treatment equipment and sensors. Read and follow the User Manuals for complete directions on how to operate this equipment (Manuals and more information available at www.GPCustomer.com/Solutions.)

Grignard Pure is to be used in full concentration and cannot be diluted.

For use only in the following listed indoor spaces (occupied or unoccupied) when adherence to current public health guidelines (e.g., CDC guidance at www.cdc.gov recommending face masks, social distancing, limited occupancy, and increased ventilation) is impractical, difficult to maintain, or is not expected to provide a sufficient level of protection. Areas of particular concern include breakrooms, locker rooms, bathrooms, lobbies, elevators, eating areas, and food preparation areas within:

- Health care facilities (e.g., hospitals, nursing homes, medical offices, dental offices), except the following*:*
  - Resident / in-patient rooms;
  - Emergency rooms including waiting areas;
  - Operating rooms;
  - Intensive care units.
- Intrastate buses, trains, and subways;
- Food processing (NAICS 311) but not food services (NAICS 722);
- Indoor spaces within buildings, including government facilities, where people are conducting activity deemed essential by the state and allowed by the state lead agency on this label, unless excluded above.

The amount of Grignard Pure product needed to maintain required levels (see Table 1) will vary depending on the following parameters (confer with your Grignard Pure-authorized dealer or Grignard Pure-certified installer to confirm specific requirements for your system):

- Size of room or interior space;
- Air exchanges per hour;
- Temperature and humidity;
- Hours of operation for your office/facility/venue.

**Standard Machine Set-up and Use**:

Machines and equipment used must be certified by Grignard Pure and-installed by Grignard Pure-certified installers. Use with any other machines, equipment, or systems is prohibited. Consult with your Grignard Pure-authorized dealer or Grignard Pure-certified installer to determine optimal installation specifications for your indoor space, to include: portable device vs. HVAC integration; number and placement of devices; sensor technology for maintaining required levels vs. visual observation.

There are two types of machine implementation and use:

**HVAC integration**: Where Grignard Pure equipment is integrated into a building's HVAC system, this installation MUST be performed by a Grignard Pure-certified installer.

Greatest efficiency is achieved when the equipment is connected directly to the HVAC unit controls, so that the equipment will turn on when the HVAC equipment has a call for operation.

**Portable device equipment**: When Grignard Pure equipment is used, the specific equipment placement shall be determined by a Grignard Pure-certified installer.

In both cases, equipment must be operated, cleaned and serviced in accordance with the User Manual.

For maximum effectiveness, the best achieved air treatment level will be reached when the temperature is between 65°F-80°F and relative humidity is between 25%-60%.

**Measuring Proper Product Concentration Levels**

Apply the product to achieve an airborne concentration of Grignard Pure according to Table 1 below.

| Measurement Method | Visual Assessment of Haze Density | Particle Sensor Reading for Grignard Pure | Equivalent Active Ingredient |
|---|---|---|---|
| Minimum | Non-visible | 0.5 mg/m³ | 0.31 mg/m³ |
| Maximum | Light Moderate | 9 mg/m³ | 5.62 mg/m³ |

There are two methods for ensuring a proper concentration of Grignard Pure in the air:

**Sensors**: Maintain a concentration between 0.5 mg/m³ to 9 mg/m³ to produce a Time Weighted Average below 4.8mg/m³ of GP [ 3mg/m³ AI] as measured by a certified sensor, purchased through an authorized dealer and installed by a certified installer. (These concentrations correspond to a range of non-visible to light moderate haze.)

**Visual Observation:** For installations where concentration is not sensor-controlled, visual assessment must replace the use of sensors. Maintain a light air treatment level by running the device for a few minutes, every 30 minutes (Times will vary depending upon the specific equipment output, and volume of space to be treated.) In this method, the observation of a very light to light haze in the air will confirm proper levels of product concentration for achieving effective, continuous levels of air treatment. Refer to www.GPCustomer.com/Visual Assessment for directions on how to effectively perform visual assessment. Recommended frequency of visual assessment monitoring is at least once every hour.

**Recommended:**

Maintain HVAC circulation at all times to ensure any Grignard Pure residue in the filter has dried out.

# Exposure Limits for Grignard Pure / TEG Established by EPA

| Measurement Method | Visual Assessment of Haze Density | Particle Sensor Reading for Grignard Pure | Equivalent Active Ingredient |
|---|---|---|---|
| Minimum | Non-visible | 0.5 $mg/m^3$ | 0.31 $mg/m^3$ |
| Maximum | Light Moderate | 9 $mg/m^3$ | 5.62 $mg/m^3$ |

**Sensors**: Maintain a concentration between 0.5 $mg/m^3$ to 9 $mg/m^3$ to produce a Time Weighted Average below 4.8$mg/m^3$ of GP [ 3$mg/m^3$ AI] as measured by a certified sensor, purchased through an authorized dealer and installed by a certified installer. (These concentrations correspond to a range of non-visible to light moderate haze.)

# Air Levels of "Glycols" in Theatrical Haze and Smoke

- Moline Study, Tables IV-10 and IV-11
  - Range of time-weighted "full-show" average concentrations: 0.015 – 1.84 $mg/m^3$
  - Range of peak exposure values across 6 shows: 0.37 – 160 $mg/m^3$ (estimated); 0.37 – 46 $mg/m^3$ (measured)
  - ➢NOTE: exposure measurements did not characterize the type of glycol exposure
- NIOSH Study, p. 3
  - "Propylene glycol was detected in samples . . ., ranging from <0.01 to 1.9 $mg/m^3$."
  - Triethylene glycol [was] detected . . ., ranging from <0.04 to 3.7 $mg/m^3$[.]"

Sources: "Health Effects Evaluation of Theatrical Smoke, Haze, and Pyrotechnics," Moline, J. M. et al. (Mt. Sinai School of Medicine & ENVIRON, 1999) (sponsored by Actors Equity Assoc.) https://www.actorsequity.org/resources/producers/safe-and-sanitary/smoke-and-haze/finalreport.pdf p. ES-3
Burr, G. A., et al. "Health Hazard Evaluation Report" (1991, 1993). https://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0355-2449.pdf

# Summary of Human Exposure to TEG from Use of Grignard Pure

The label approved by EPA establishes limits on the concentration of TEG in a treated space, as well as the duration of exposure:

- Minimum concentration of TEG – 0.31 mg/ $m^3$
- Maximum concentration of TEG – 5.62 mg/ $m^3$
- Time-weighted average concentration of TEG – 3 mg/ $m^3$
- Duration of exposure to TEG – no more than 12 hrs./day

EPA-approved exposures to TEG from use of Grignard Pure are generally less than or comparable to exposures resulting from use of TEG-based lighting effects products in theatrical productions and in TV and film industries

# Other Government and Independent Safety Assessments of Triethylene Glycol

# Outline of Safety Presentation (2)

- Evaluating Inhalation Exposure to TEG
- **Government & Independent Safety Assessments**

| ANSI | |
|---|---|
| Moline, et al. | EPA Safer Chemicals Program |
| UN International Labor Organization | Food & Drug Administration |
| EPA Pesticide Office | Intrinsik |

- Preliminary Inhalation Risk Assessment for Use of Grignard Pure
- Conclusions

# ANSI, Moline, and ILO Safety Reviews

- ANSI Air Quality Standard E1.5 - Theatrical Fog Made With Aqueous Solutions Of Di- And Trihydric Alcohols
  - Time-Weighted Average – 10 mg/m$^3$ for “glycols”
  - Peak exposure limit – 40 mg/m$^3$
- Moline, et al. Study, p. VI-10.
  - “The [recommended] exposure concentration of 12.5 ppm [for “glycols”] is equivalent to . . . 77 mg/m$^3$ triethylene glycol . . ..”
- ILO Chemical Safety Cards
  - Threshold Limit Value – 1,000 mg/m$^3$

Sources: NIH PubChem database for TEG; Moline Study

# 2013 EPA Pesticide Reevaluation Program – TEG

- In the . . . Propylene Glycol and Diproylene Glycol RED and the . . . Triethylene Glycol RED, the Agency concluded that propylene glycol, dipropylene glycol, and triethylene glycol pose no toxicological concerns due to their low toxicity; therefore, no toxicological endpoints of concern were developed. Based on a review of the available toxicity data (see Appendix A), the agency concludes that for registration review these chemicals pose no toxicological concerns when used according to pesticide labeled uses. No additional toxicity data requirements are anticipated at this time for registration review. This conclusion is based on the results of toxicity testing of propylene glycol and dipropylene and triethylene glycol at dose levels near or above testing limits . . ..” [p. 13]

Source: EPA Propylene Glycol, Dipropylene Glycol, and Triethylene Glycol Preliminary Work Plan (2013), available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0219-0002

# TEG is Safe to Use Around Food

## Exemption From the Requirement of a Pesticide Tolerance

- Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement of a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the exemption is "safe," i.e., there is a "reasonable certainty of no harm"
- Although the current uses have the potential to result in exposure to residues of dipropylene and triethylene glycol in or on food, including uses of these chemicals as inert ingredients, the low order of toxicity and low application rates from the current uses of these chemicals support a conclusion that exemptions from the requirement of a tolerance for these pesticide chemicals when used in antimicrobial formulations on food-contact surfaces in public eating places, on dairy processing equipment, and on food processing equipment and utensils would be safe.

Source: https://www.govinfo.gov/content/pkg/FR-2020-05-22/pdf/2020-10805.pdf

# Other Government Safety Reviews

- EPA's "Safer Chemicals" program
  - TEG is recognized as a "Green Circle" material, i.e., "The chemical has been verified to be of low concern based on experimental and modeled data." Source: https://www.epa.gov/saferchoice/safer-ingredients
- Food & Drug Administration
  - TEG & PG – approved as "indirect food additives" in certain "food contact substances" Source, e.g., : 21 CFR 175.105, 175.300, 175.320, .1200, 177.1390, .3740, and .3910
- No OSHA, NIOSH, ACGIH, CPSC limits for TEG

# Intrinisk Toxicology Risk Assessment

"Based on available data, *Grignard Pure* MEETS the requirements for classification as not toxic (acute/chronic), corrosive, a skin/eye irritant, or a strong sensitizer as defined in 16 CFR 1500.3, when used as intended or under circumstances involving reasonable foreseeable misuse. In addition, the ingredients in the product are not included in the list of banned hazardous substances cited in 16 CFR 1500.17"

Source: Intrinsik Toxicology Risk Assessment – Grignard Pure, May 6 2020

# Intrinsik Toxicology Risk Assessment

- Assessment of triethylene glycol (CAS No. 112-27-6) was based on consideration of available animal data and human experience/use information.
- According to the European Chemicals Agency's Classification and Labelling Inventory database, triethylene glycol (listed as 2,2'-(ethylenedioxy) diethanol) has not been classified for human health hazards by the majority of industry notifiers.

Source: Intrinsik Toxicology Risk Assessment – Grignard Pure, May 6 2020

# Intrinsik Toxicology Risk Assessment

- Triethylene glycol is listed in the EU Cosmetic Ingredients and Substances database with no use restrictions. Triethylene glycol is also listed as an indirect food additive by the US FDA (multiple 21 CFR listings).
- Additionally, triethylene glycol is listed in the Health Canada Natural Health Products Ingredients Database as a non-medicinal ingredient for topical application.
- Based on the available information, triethylene glycol is not considered to pose a safety concern at the concentration present in the product.

Source: Intrinsik Toxicology Risk Assessment – Grignard Pure, May 6 2020

# Preliminary Inhalation Risk Assessment for TEG from Use of Grignard Pure – How would exposure compare to a safe level?

# Outline of Safety Presentation (2)

- Evaluating Inhalation Exposure to TEG from use of Grignard Pure
- Government & Independent Safety Assessments
- **Preliminary Inhalation Risk Assessment for Use of Grignard Pure**
  - Point of Departure for chronic systemic effects
  - Uncertainty factors
  - Recommended safe level for chronic inhalation exposure
- Conclusions

# Determining a Point of Departure for TEG (1)

"Upon reviewing the available toxicity information, the Agency has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to triethylene glycol. This conclusion is based on the results of toxicity testing of triethylene glycol in which dose levels near or above testing limits . . . were employed in experimental animal studies and no significant toxicity observed."

- Acute Eye Irritation of concentrated TEG – mild, quickly reversible eye irritation
- **Acute Inhalation Toxicity – LC 50 greater than 5.2 mg/L = 5200 mg/$m^3$ – RED, p. 8;**

"Repeat dose toxicity studies by the oral, dermal, and inhalation routes at doses near or above the limit doses for such studies (1000 mg/kg/day for oral and dermal studies, 1000 mg/$m^3$ for inhalation studies) have also shown a lack of systemic toxicity or toxicity only at doses in excess of the limit dose. . . . Chronic exposure of experimental animals to triethylene glycol at doses equivalent to or in excess of the limit dose for such studies has shown the chemical to be without adverse toxic effects. [pp. 6 – 7.]

➢ EPA Memorandum "***TRIETHYLENE GLYCOL:*** Revised Antimicrobials Division's Review of the Disciplinary Sciences for Issuance of the Reregistration Eligibility Decision (RED) Document." available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2005-0250-0002

# Determining a Point of Departure for TEG (2)

- Determine the appropriate toxicity study (or studies) for identifying the smallest amount of exposure that causes harm, and then find the next lowest dose at which no harm occurs
  - An appropriate study is matched to human experience by duration and route of exposure because safe “acute” exposures are generally safer than multi-day exposures
- Based on the toxicity data for TEG, we choose the toxicity value from the multi-day, inhalation toxicity study [EPA Toxicity Review, p. 39]
  - This is a cautious or conservative choice because this study would replicate a “high end” exposure scenario:  multiple days of nose-only inhalation of high concentrations of the chemical

Our recommended POD for TEG is the 1036 $mg/m^3$ dose used in the Ballantyne inhalation toxicity study

# Safety Factors for TEG

- Estimating a “safe dose” from animal toxicity studies involves some types of Safety Factor (Uncertainty Factor – UF). To account for what is not known, EPA divides the POD , the lowest level that causes no harm to test animals, by “uncertainty factors” [UF], specifically:
  - Humans may be more sensitive than animals [10X UF]
  - Human sensitivity is likely to vary [10X UF]
  - Uncertainty due to an incomplete database [3X-10X UF]
- For TEG, because there is a complete toxicity database,we decided to use a total UF of 100 [10 x10] for the potential that humans are more sensitive than test animals and because humans can vary in their sensitivity

# Recommended Safe Lifetime Inhalation Exposure Limit for TEG

- Recommended safe dose level = Point of Departure + Uncertainty Factor
- For TEG, my recommended safe chronic inhalation exposure is: 10mg/m³ = 1036 mg/m³ (POD) ÷ 100 [UF]
- My recommendation is:
  - Equal to the TWA level recommended by ANSI for all “glycols.” many of which are more toxic than TEG
  - 4 times lower than the peak level recommended by ANSI for glycols
  - 7 times lower than the peak level recommended by Moline, et al

# Comparison of TEG Exposure with Recommended Safe Inhalation Exposure Limit

- Using our recommended safe inhalation exposure limit (**10 mg/m$^3$**), it is plain that use of Grignard Pure – and the resulting exposure to TEG at a Time-Weighted Average of **3 mg/m$^3$** – will not pose risks of concern for systemic effects.
- Use of Grignard Pure may cause transient, mild irritation of eyes, nose, and throat in some sensitive individuals

# Conclusions

# Safety of Grignard Pure

1. Government agencies (EPA, FDA) have judged TEG to be “low risk” when used in products regulated by the agencies.

2. Inhalation exposure to TEG from use of Grignard Pure would be below recommended safe exposure limits and hundreds of times lower than the concentration that caused no systemic effects in inhalation toxicity studies with laboratory animals.

3. Exposure to TEG aerosol may cause transient, mild irritation of eyes, nose, or throat in some sensitive individuals

# Thank you