Proposed Registration Decision for the New Active Ingredient Glycerol Formate

Approved by: Digitally signed by EDWARD MESSINA Date: 2024.09.06 11:21:35 -04'00'

Ed Messina, Esq.
Director, Office of Pesticide Programs
US Environmental Protection Agency

Table of Contents

I. SUMMARY

The U.S. Environmental Protection Agency (referred hereafter as EPA or The Agency) is proposing to register under section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), a manufacturing use product (MUP) and end use product (EP) for use in/on medical premises and equipment containing the active ingredient (A.I.), glycerol formate.

Ecolab, Inc. submitted a registration package that includes one MUP (919789, EPA Reg. No. 1677-EAL, 99.83% active ingredient purity) and one end-use product (EP) (DuoGuard RTU, EPA Reg. No. 1677-EAA). Glycerol formate is a blend comprised of 45-60% glycerol triformate, 36-48% diformate, and 0-10% monoformate. Glycerol formate reacts with hydrogen peroxide to form performic acid (PFA), the active biocide.

The EP is intended to be used as a hospital sporicidal disinfectant for non-porous, non-food contact hard surfaces and as a sanitizer for soft surfaces in healthcare settings (e.g., hospitals, medical premises/equipment, and nursing homes). The proposed product is a two-part system where Part A (containing glycerol formate) is contained in a sealed bottle cap and Part B (containing hydrogen peroxide) is contained in a sealed bottle. To create the end use solution, the label directions state: "twist the dosing cap on the bottle to align notch, then press down to break inner seal so that the soultion in the cap fully releases into the bottle. Shake vigorously for 30 seconds to fully mix solution" (label dated 5/9/2022). The end use solution containing PFA is then poured into a container and applied with a wipe to disinfect surfaces.

II. REQUESTED ACTION

On October 11, 2019, the EPA received an application from Ecolab, Inc. for registration of two products containing a new A.I., glycerol formate (PC Code 087803). The proposed products are an MUP and an EP. The proposed MUP is only for formulation into an antimicrobial pesticide product for nonfood uses on medical premises and equipment such as the nonfood areas of hospitals/medical institutions, nursing homes/assisted living facilities, and noncritical patient care items and noncritical environmental surfaces. The proposed glycerol formate EP product is labeled for use as a sporicidal disinfectant for use on non-porous, non-food contact hard surfaces and as a sanitizer for soft surfaces in healthcare settings.

III. USE PROFILE

Table 1. Summary of Directions for Proposed Uses of Glycerol Formate

Proposed Use Pattern for EP	Product Application Rates
Disinfectant for use on non-porous, non-food contact hard surfaces and as a sanitizer for	Two-part system: Part A 99.7% Glycerol Formate Part B 1.1% Hydrogen Peroxide

Proposed Use Pattern for EP	Product Application Rates
soft surfaces in healthcare settings. Use sites include hospitals, medical premises/equipment, and nursing homes/assisted living facilities. Hard surfaces include non-critical and semi-critical stainless-steel instruments, toilet bowls, walls, bathrooms, etc., while soft surfaces include cotton or polyester sheets, towels, and upholstery.	Part A and Part B are mixed to generate PFA *in situ* Application rates: 1.1% H_2O_2 and 800 ppm PFA, with a target PFA concentration of at least 300 ppm throughout the use life (up to 60 minutes).

IV. EVALUATION

In evaluating a pesticide registration application, the EPA assesses a wide variety of information including directions for use (i.e., where and how the pesticide is used), environmental fate (i.e., how the chemical will move in the environment), and toxicity studies (i.e., effects on humans and other non-target organisms) to determine the likelihood of adverse effects (i.e., risk) from exposures associated with the proposed use of the product. Risk assessments are developed to evaluate the environmental fate of the compound as well as how it might affect a wide range of non-target organisms including humans, terrestrial and aquatic wildlife (plants and animals). The risk assessment also evaluates the impact of the pesticide to all listed species and designated critical habitats under the Endangered Species Act (ESA). Based on these assessments, the EPA evaluates and approves language for each pesticide label to ensure the directions for use and safety measures are appropriate to mitigate any potential risk. In this way, the pesticide label communicates essential limitations and mitigations that are necessary for public safety. It is a FIFRA violation to use a pesticide in a manner inconsistent with its labeling.

The EPA requires a wide range of studies to assess a pesticide's use scenario. For the proposed use of glycerol formate, the database of studies required to support the assessment of risk to human health and the environment is adequate.

A. Assessment of Risks to Human Health

Although glycerol formate is the active ingredient in the channels of trade, applicators and bystanders will primarily be exposed to the PFA solution. Since the Agency does not have mammalian toxicology data on PFA, the Agency is relying on the peroxy compounds toxicology database to assess the potential risks from exposure to PFA when used as a disinfectant on hard nonporous surfaces and as a sanitizer on soft surfaces. The peroxy compounds toxicology

database is considered adequate and therefore, the database required to evaluate the human health effects of PFA is considered adequate as well. This section summarizes the Agency's Human Health Risk Assessment. The full Human Health Risk Assessment can be found in EPA's public docket (EPA-HQ-OPP-2020-0120) at www.regulations.gov.

1. Toxicology Summary

Since the Agency does not have mammalian toxicology data for PFA, the Agency assembled a partial read-across for performic acid (PFA), peracetic acid (also known as peroxyacetic acid; PAA), and hydrogen peroxide (H_2O_2) and concluded that PFA may be grouped with the peroxy compounds based on PFA's structural similarity to PAA and to a lesser extent H_2O_2 on the basis that all are oxidants with a highly reactive peroxy functional group.

Acute toxicity data are not available for technical grade performic acid. However, the available acute toxicity information on peracetic acid indicates that it is of low oral and moderate dermal and inhalation toxicity (Toxicity Category III and II, respectively), yet is corrosive and a severe eye irritant (Toxicity Category I).

The Food and Drug Administration (FDA) has designated hydrogen peroxide as Generally Recognized as Safe (GRAS; 21 CFR §184.1366). Hydrogen peroxide is also found in the human body and can play an important role in cellular defense. The two main cellular enzymes involved in breakdown of hydrogen peroxide are catalase and glutathione peroxidase. Hydrogen peroxide rapidly dissociates into oxygen and water. Based on this information the Agency does not have a concern for mutagenicity or carcinogenicity from the oral route of exposure.

However, the Agency cannot make the same determination of no mutagenicity and carcinogenicity concerns via the inhalation route, as PFA (along with the other peroxy compounds) is a member of the reactive oxygen species family which are irritants in the lung and respiratory tract and can cause oxidative stress damage to several biological systems resulting in inflammation, cardiovascular disease, and ischemia as well as DNA damage and cancer. Hydrogen peroxide is volatile, with a vapor pressure of ~1-5 mmHg (value highly dependent on concentration and temperature). The average half-life of hydrogen peroxide in air is about 1 day (US EPA, 2007).

There are two inhalation studies (28-day rat and 90-day rat) on hydrogen peroxide that were critical for endpoint selection and establishing the Point of Departure (POD) for the inhalation risk assessment. The 90-day inhalation rat study established the No Observed Adverse Effect Concentration (NOAEC) of 9.95 mg/m^3 at the highest concentration tested because no effects were observed in the study. The Lowest Observed Adverse Effect Concentration (LOAEC) of 14.6 mg/m^3 is based on the necrosis and inflammation of squamous epithelium in the anterior of the nasal cavity observed in the 28-day inhalation rat study. Of note, hemorrhage and lung inflammation was also observed in the 28-day study in at least one animal in each treated group along with other effects in the nasal cavity and larynx.

i. FQPA Safety Factor

The FQPA Safety Factor (as required by the Food Quality Protection Act of 1996) is intended to provide an additional 10-fold safety factor (10X) to protect for special sensitivity in infants and children to specific pesticide residues in food, drinking water, or residential exposures, or to compensate for an incomplete database. As glycerol formate and PFA have no proposed food uses and all proposed uses are indoors with a low likelihood of environmental exposure in drinking water to glycerol formate and PFA, there are no potential dietary exposures from the proposed uses, and therefore, the Food Quality Protection Act (FQPA) does not apply.

ii. Selecting Endpoints and Points of Departure (POD)

POD and endpoint selection for oral exposures (any duration, dietary or incidental) are not needed as there are no oral exposures based on the proposed use pattern for glycerol formate. Dermal exposures can occur, particularly when using a concentrated product. However, the percentage of active ingredient in the end use product is low enough that dermal acute toxicity is not expected.

For hydrogen peroxide, which is highly water-soluble, the effects of concern from inhalation exposures are limited to the extra-thoracic region including necrosis and inflammation of squamous epithelium in the anterior nasal cavity. In accordance with the EPA guidance document "*Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment*" (EPA, 2012a), the Agency concluded that the peroxy compounds should be classified as Category 1 gases (highly water-soluble, highly reactive). In calculating the human equivalent concentration (HEC), the regional gas deposition ratio (RGDR) of 1 was assumed.

As noted in the 28-day inhalation study, the effect of necrosis and inflammation of the epithelium in the anterior regions of the nasal cavity is considered an irritant effect. Compared to systemic adverse effects, irritation and/or corrosion responses are not expected to show as large of a variation in severity and duration of response between or among mammalian species. In addition, direct irritation and/or corrosivity effects are more dependent on the concentration at the site(s) of contact compared to the duration of contact, in contrast to systemic toxicity, which is driven by the overall body burden of the chemical. Thus, irritant and/or corrosion effects do not typically increase in severity with continued exposure, and variation among species or within species is not expected to show as large of a variation in response as can be observed with systemic effects. Based on recommendations published by the National Research Council (NRC, 2001), for direct-acting irritants and corrosives that do not show systemic toxicity as the primary toxic effect, the Uncertainty Factor (UF) UF_A and UF_H can be reduced from 10x to 3x for a total UF of 10x. Increased sensitivity to children was not observed in the toxicity database and the POD based on irritant effects is considered protective of systemic effects. For performic acid, utilizing the HEC, a total UF of 100x is applied for all inhalation exposure durations. This UF includes the UF_A of 3x for interspecies variation and the UF_H of 3x for intraspecies variation as discussed above. In addition, a UF_{DB} of 10x (database uncertainty) is

included to account for the uncertainties from utilizing hydrogen peroxide toxicity data to assess the toxicity of PFA.

Table 1. Toxicological Doses and Endpoints for the Peroxy Compounds, PFA and PAA

Exposure Scenario	POD for Risk Assessment	Target MOE[D]	Studies and Observed Effects (both studies are co-critical)
Performic Acid (Inhalation, All durations[A])	NOAEC = 10 mg/m^3 (7.1 ppm) 8 Hour HEC[B] = 7.5 mg/m^3 (5.4 ppm[C]) 24 Hour HEC[B] = 2.5 mg/m^3 (1.8 ppm[C])	$UF_{A=}$ 3 UF_H = 3 UF_{DB} = 10 LOC = 100 (Target MOE)	28-day hydrogen peroxide rat inhalation study (CEFIC Peroxygen Sector Group, 2002) 90-day hydrogen peroxide rat inhalation study (MRID 49469301) NOAEC = 10 mg/m^3 (highest dose tested from the 90-day study). LOAEC = 14.6 mg/m^3 (mid-dose from the 28-day study) based on the necrosis and inflammation of squamous epithelium in the anterior of the nasal cavity (3/5 M and 2/5 F).

A. Includes Short Term (1 to 30 days), Intermediate Term (30 to 180 days) and Long Term (more than 180 days)
B. HEC = NOAEC (mg/m^3) * Animal Exposure * (6 hrs/day) / Human Exposure * (8 or 24 hrs/day) * RGDR (1.0)
C. 1 ppm = 1.4 mg/m^3 based on the hydrogen peroxide molecular weight of 34.01 g/mol.
D. These target MOEs apply to both occupational and residential exposures.

Point of Departure (POD) = A data point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEC = no observed adverse effect concentration. LOAEC = lowest observed adverse effect concentration.
HEC = human equivalent concentration. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). $UF_{DB=}$ use of hydrogen peroxide studies to assess toxicity of PAA and PFA. MOE = margin of exposure. LOC = level of concern. RGDR = regional gas dose ratio

2. Exposure Risk Characterization Summary

i. Dietary Exposure Risks

There are no proposed food uses for glycerol formate. Additionally, all proposed glycerol formate uses are indoor with a low likelihood of environmental exposure in drinking water. Therefore, no dietary exposures are expected.

ii. Occupational Handler Exposure Risks

There is the potential for long-term occupational handler inhalation exposure to PFA during the application of the proposed product in health care facilities, where surface treatment applications are conducted daily. Exposure is to PFA, which, according to the proposed labels, remains efficacious for up to approximately one hour from the time the ingredients are combined. It is anticipated that workers will mix and use several batches of product per day. The product is applied via clean cloth to wet hard, non-porous surfaces. Occupational workers are required to wear gloves when using/applying the solution. The inhalation margin of exposure (MOE) for this use pattern is 110 and not of concern because it is greater than the long-term level of concern (LOC) of 100.

iii. Post-Application (Bystander) Exposure Risks

There is the potential for residential bystander (i.e., patient adult or child) inhalation exposure to performic acid during the application of the proposed product. The patient could be exposed to the product if it is used in occupied rooms. The 24-hour time-weighted average (TWA) exposure for a patient occupying a room during and after treatment was calculated, and the air concentration data for the first 60 minutes was used to represent the first hour of exposure. One half the limit of detection (LOD) of 0.003 ppm was used to represent 23 hours of exposure. Based on the 24-hour TWA of 0.003 ppm, the MOE is 600 which is not of concern because it is greater than the LOC of 100. For this assessment, the air concentrations are utilized as a health protective screen, and no dose calculations are needed to account for population subgroups including children.

iv. Aggregate Exposure Risks

There are no anticipated dietary exposures from the proposed product, thus there is no need for an aggregate exposure characterization.

v. Cumulative Risks

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to Glycerol Formate, and any other substances, and Glycerol Formate do not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, EPA has not assumed that Glycerol Formate

has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[1] and conducting cumulative risk assessments (CRA)[2].

3. Human Health Incidents

Because glycerol formate is a proposed new active ingredient, there are no human health incidents reported in the database. However, since the primary exposures are to PFA, which can be produced by other currently registered chemicals (i.e., hydrogen peroxide and formic acid), the Incident Data System (IDS) was searched for incidents relevant to the proposed uses of glycerol formate. Reported incidents exist for products where formic acid or hydrogen peroxide is the active ingredient; however, it is unclear how these reported incidents relate to the proposed glycerol formate use patterns and the resulting exposure.

i. Formic Acid

Based on a search of the IDS for formic acid from April 2019 to April 2024, no incidents were reported.

ii. Hydrogen Peroxide

Based on a search of the IDS for all peroxy compounds from April 2019 to April 2024, there were 109 discrete reports. Of these, there were no reported deaths, and 10 incidents were reported as "major." Major incidents included chemical burns and respiratory symptoms.

In addition to the incidents reported in the IDS, hospital employee complaints of respiratory irritation were investigated by the National Institute for Occupational Safety and Health (NIOSH) in two Health Hazard Evaluations (HHEs). Both these HHEs were conducted at hospitals where a peroxy product (OxyCide, EPA Reg. No. 1677-237), which contains 27.5% hydrogen peroxide and 5.8% peracetic acid, was diluted at the rate of 3 ounces per gallon and applied via wipes to clean and disinfect hard surfaces. In HHE 2015-0053-3259 (NIOSH, 2018), NIOSH found that increased exposure to hydrogen peroxide, peracetic acid and acetic acid vapors were associated with increases in acute work-related nasal and eye symptoms and increased shortness of breath on level ground reported by cleaning staff. In HHE 2017-0114-3357 (NIOSH, 2019), NIOSH reported similar findings regarding increased exposure to hydrogen peroxide, peracetic acid or

[1] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (EPA, 1999)
[2] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (EPA, 2002)

acetic acid and symptoms reported by hospital staff. In both HHEs, NIOSH provided recommendations to reduce exposure. These recommendations included calibrating the product dispensers to properly dilute the product to maintain a pH of 2.7 to 4.0 and minimizing the use of the product in non-patient care areas.

B. Assessment of Environmental and Ecological Risks

Ecological risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic (RQ = Exposures/Toxicity). RQs are then compared to the EPA's levels of concern (LOCs). The LOCs are criteria used by the EPA to indicate potential risk to non-target organisms. The criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to non-target organisms.

As stated previously, primary exposure is to PFA, formed by the reaction of glycerol formate and hydrogen peroxide, and may occur when spent solution is discarded down the drain. In the environment, PFA is expected to degrade very rapidly to formate/formic acid and hydrogen peroxide (which in turn rapidly degrades into oxygen and water), resulting in limited environmental exposure.

If any environmental exposure to the glycerol formate occurs (e.g., in the PFA solution, which initially contains 1% glycerol formate, or in cases of spills), glycerol formate hydrolyzes rapidly to glycerol and formate/formic acid. Should any glycerol formate be released into the environment, glycerol formate and its degradates have low persistence and are expected to result in limited environmental exposure as well.

The proposed EP contains inert ingredients that are meant to stabilize the PFA for the duration of use (e.g., ~1 hr after mixing glycerol formate with hydrogen peroxide). Any environmental exposures are expected to be negligible because by the time the spent solution is discarded down the drain, the PFA would have degraded into oxygen and water even in the presence of the stabilizers.

Therefore, risks to nontarget terrestrial and aquatic organisms from exposure to PFA formed during the proposed antimicrobial use of glycerol formate as an indoor hospital disinfectant are expected to be negligible. The Agency is making a "no effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitats for such species based on the expected negligible exposure from the antimicrobial use of glycerol formate.

1. Environmental Fate

i. PFA

Various environmental fate guideline studies have been submitted for glycerol formate, but none were submitted for PFA, the final active biocide form. However, public literature data are available for PFA. Given its vapor pressure (11.2 mmHg at 25°C, i.e., $\geq 10^{-6}$ mmHg criteria[3]) and Henry's Law Constant ($<10^{-5}$ atm-m^3/mol; i.e., $\geq 10^{-7}$ atm-m^3/mol criteria[4]) from Table 1, PFA is expected to volatilize readily from dry surfaces and aqueous solutions. Hydrolytic half-lives were estimated to be 4 minutes at pH 7 and 0.4 minutes at pH 8 (Mill *et al*., 1987). Additionally, a white paper on PFA in oilfield uses indicates that PFA is highly reactive with metals and organic matter, and it is expected to degrade very rapidly to formate/formic acid and hydrogen peroxide in the environment; the observed half-lives of PFA were <6 minutes in produced water and ~60 minutes in distilled water (MRID 50705607; reviewed by US EPA, 2019b[5]).

Using the available information for PFA, PAA, and hydrogen peroxide, EPA assembled a partial read-across and determined that PFA may generally be grouped with the peroxy compounds (Appendix D of the risk assessment). More details on the fate profile for the peroxy compounds can be found in the Peroxy Compounds DRA (US EPA, 2022), which assesses risk of exposure from hydrogen peroxide, PAA, peroxyoctanoic acid, and sodium percarbonate. According to the Peroxy Compounds DRA (US EPA, 2022), peroxy compounds readily hydrolyze and rapidly break down to hydrogen peroxide (which in turn rapidly degrades into oxygen and water upon contact with organic matter) and respective associated acid/salt compounds. Furthermore, hydrogen peroxide has a half-life of 2 minutes in wastewater treatment plants (WWTPs) with an estimated removal of over 99% during wastewater treatment, biodegrading to water and oxygen prior to discharge from WWTPs (EU, 2003, as cited in US EPA, 2022). As a result, no significant exposure is expected for PFA in the environment, and no additional environmental fate data are required.

ii. Glycerol Formate

Although primary exposure is expected to be to PFA, this section also discusses the environmental fate data for the proposed new active ingredient, glycerol formate, as the registrant indicated that the final PFA solution will initially contain 1% glycerol formate (MRID 50864540).

Glycerol formate, in this risk assessment, is comprised of glycerol monoformate, diformate, and triformate, with the triformate species being the predominant species. Based on Table 1 in the

[3] 10^{-6} mmHg is the general criteria for volatility from dry, non-adsorbing surfaces, based on OCSPP 835.6100, US EPA (2013), and US EPA (2021).
[4] 10^{-7} atm-m^3/mol is the general criteria for volatility from wet surfaces (*i.e.*, water and moist soil), based on OCSPP 835.6100, US EPA (2013), and US EPA (2021).
[5] US EPA (2019) erroneously reported the half-life to be 15-30 minutes in deionized water. The study (MRID 50705607) indicates the half-life to be ~60 minutes in distilled water (not deionized water).

risk assessment, glycerol formate has a high vapor pressure of 0.219 mmHg (i.e., $\geq 10^{-6}$ mmHg criteria3), indicating that it will volatilize from dry surfaces. Volatility from wet surfaces, on the other hand, may be limited due to low estimated Henry's law constant of $<10^{-8}$ atm·m^3/mol (i.e., $<10^{-7}$ atm-m^3/mol criteria4).

As indicated in Table 8 below, hydrolysis of glycerol formate at 25°C is rapid with a half-life of ≤1.88 days at pH 4, with more rapid degradation at higher pH values (≥pH 7). The hydrolytic instability is consistent with the chemical structure containing hydrolyzable ester groups. Due to its structural similarity with glycerol triacetate (or more commonly called triacetin, CAS No. 102-76-1), which hydrolyzes in successive steps to diacetin, monoacetin, and finally acetate (or acetic acid) plus glycerol, glycerol formate (as the tri-ester form) is expected to hydrolyze similarly to diformate, monoformate, and finally formate/formic acid plus glycerol (MRID 51054201; OECD, 2002; Yamasaki, 1920). The major degradation products are expected to be glycerol and formate/formic acid. With a log K_{ow} of -0.84, glycerol formate is not expected to significantly bioaccumulate in fish (Table 1 of the risk assessment).

Persistence in aquatic and soil environments is low for glycerol formate and its degradates. Glycerol formate is mobile to highly mobile in soil, based on a log K_{oc} value of <1.25 in a non-guideline high-performance liquid chromatography (HPLC) study. However, contact with soil is expected to be insignificant, as the proposed use pattern of glycerol formate does not result in direct or indirect (through residues in land-applied sludge) applications to soil, and glycerol formate rapidly hydrolyzes to glycerol and formic acid/formate. Glycerol formate is also readily biodegradable, and open literature (as cited in MRIDs 50864534, 50864535, and 50864540) indicates the degradates are also biodegradable under aerobic and anaerobic conditions and are metabolized by microorganisms in many important biochemical processes.

Activated sludge respiration inhibition (ASRI) data were submitted for glycerol formate and demonstrate a high half-maximal inhibitory concentration (IC_{50} = 198.8-514.6 mg/L; i.e., >20 mg/L), indicating the unlikelihood of any adverse effects of glycerol formate on activated sludge microorganisms.

Table 8 below summarizes the environmental fate guideline studies submitted for glycerol formate and PFA.

Table 8. Environmental Fate Data for Glycerol Formate and PFA

Guideline No. (GLN)	Guideline Study Name	Glycerol Formate	PFA
835.2120	Hydrolysis	At 25°C: pH 4: $DT_{50} \leq 1.88$ days pH 7: $DT_{50} \leq 0.0477$ days (69 min)	pH 7: 4 minutes pH 8: 0.4 minutes (Mill *et al*., 1987) Produced water: <6 minutes

Guideline No. (GLN)	Guideline Study Name	Glycerol Formate	PFA
		pH 9: DT_{50} < 0.0104 day (15 min) (MRID 50864530; acceptable; US EPA, 2020)	Distilled water: ~60 minutes (MRID 50705607; US EPA, 2019b)
835.3110	Ready Biodegradability	Readily biodegradable (80% CO_2 evolution after 10 days; 83-86% CO_2 evolution on days 14-28); non-toxic to WWTP microorganisms (MRID 50864533; acceptable; US EPA, 2020)	Sludge biodegradation: No data, but DT_{50} is expected to be faster than for PAA) (PAA DT_{50} = 3 minutes; EU, 2015, as cited in US EPA, 2022)
850.3300	Activated Sludge Respiration Inhibition (ASRI)	IC_{50} = 198.8-514.6 mg/L (*i.e.*, >20 mg/L); not expected to be toxic to WWTP microorganisms (MRID 50864532; supplemental; US EPA, 2020)	No data
Non-guideline	Estimation of Adsorption Coefficient (K_{oc}) by HPLC	Log K_{oc} <1.25; mobile to highly mobile in soil (MRID 50864536; satisfies OCSPP 835.1230 Adsorption/Desorption guideline requirement)	No data

Although PFA may be released into the waste stream after use in sinks or when the spent solution is discarded down the drain, it will rapidly hydrolyze to formic acid/formate and hydrogen peroxide (which in turn rapidly degrades into oxygen and water upon contact with organic matter), minimizing any exposure to wastewater. Based on Table 7 in the risk assessment, the hydrolytic half-lives of PFA are 0.4 to ~60 minutes, and in wastewater with microorganisms present, PFA is expected to degrade more rapidly. Public literature supports this rapid degradation of PFA, in which PFA, at 2.5 ppm, demonstrated half-lives ranging from 33 minutes (12°C) to 13 minutes (25°C) in WWTP wastewater discharge[6].

iii. Degradates of Potential Concern

PFA is extremely reactive with metals and organic matter and must be generated on-site by mixing glycerol formate and hydrogen peroxide. As a highly unstable strong oxidant, PFA degrades rapidly in the environment to formate/formic acid and hydrogen peroxide (which in turn rapidly degrades into oxygen and water upon contact with organic matter) and presents minimal concerns to the environment.

[6] Rocher, V.; Azimi, S.; Mailler, R.; Rechdaoui-Guérin, S.; Mèche, P.; et al. (2021). Effectiveness of Disinfecting Wastewater Treatment Plant Discharges: Case of chemical disinfection using performic acid. IWA Publishing, 9781789062090. https://hal-enpc.archives-ouvertes.fr/hal-03201270v1/document

If any environmental exposure (terrestrial or aquatic) to glycerol formate occurs (e.g., when the PFA solution, which initially contains 1% glycerol formate, is disposed of down the drain), glycerol formate is expected to degrade rapidly to glycerol and formate/formic acid. These degradation products present minimal concerns to the environment. Glycerol is found in triglycerides, which are main constituents of vegetable and animal fats and oils and is part of many important biochemical processes. Formic acid is a simple carboxylic acid that is ubiquitous in the environment and is found in plants, animals, soil, surface water, and the atmosphere. It is also an important metabolic intermediate. Formic acid/formate is a common product of bacterial fermentation and does not accumulate under oxic conditions (Lim *et al.*, 2014), suggesting it transforms readily. Oxidation of formic acid/formate under aerobic conditions yields carbon dioxide and water. In addition, both glycerol and formic acid have been classified by the Food and Drug Administration as generally recognized as safe (GRAS), suggesting limited toxicity from dietary exposure.

2. Ecological Effects and Risks

The registrant has submitted five guideline studies as well as waiver requests for the additional ecotoxicity data for glycerol formate, as outlined in the 40 CFR §158W. All studies have been reviewed, and all waiver requests were granted. Glycerol formate is practically non-toxic to birds and freshwater invertebrates, and slightly toxic to freshwater fish.

Due to the instability of PFA and the proposed indoor use of the glycerol formate EP, the potential for environmental exposure to PFA is expected to be limited. Therefore, no ecotoxicity data on PFA has been submitted to the Agency. That said, similar to human health toxicity, PFA may generally be grouped with the peroxy compounds. The toxicity profile of peroxy compounds indicates that they are generally more toxic to aquatic organisms than glycerol formate. Depending on the compound tested and whether it was tested in the form of a product or TGAI, peroxy compounds are slightly toxic to birds, practically non-toxic to bees, practically non-toxic to highly toxic to freshwater fish, moderately toxic to estuarine/marine fish, slightly to highly toxic to freshwater invertebrates, moderately to highly toxic to estuarine/marine invertebrates, and moderately to highly toxic to bivalves. In addition, decreases in cell density in vascular plants and non-vascular aquatic plants above 1 mg/L were observed. For more details on the ecotoxicity of peroxy compounds, see the registration review documents within docket EPA-HQ-OPP-2009-0546 at www.regulations.gov.

i. Aquatic Exposure

No aquatic exposure modeling was performed in EPA's risk assessment because all registered antimicrobial uses of glycerol formate are considered indoor with a low likelihood of environmental exposure. In the event that PFA is released into a waste stream, the Agency believes that it will volatilize and degrade rapidly and, therefore, pose limited exposure potential to wastewater treatment plants, surface water, and groundwater. Thus, no adverse

impacts to nontarget plants and wildlife are expected, and only a qualitative ecological risk assessment was conducted for the antimicrobial uses of glycerol formate.

ii. Ecological Risk Characterization

Based on the proposed indoor use pattern, high volatility, and rapid degradation in the environment, terrestrial and aquatic exposures to PFA are not expected when the product is used according to label specification. As a result, the Agency does not anticipate any adverse effects to nontarget organisms from the indoor uses of the proposed new active ingredient, glycerol formate.

iii. Ecological Incident Data

Glycerol formate is a proposed new active ingredient; therefore, there are no reported ecological incidents. However, since the primary exposures are to PFA, which can be produced by other currently registered chemicals (i.e., hydrogen peroxide and formic acid), the Incident Data System (IDS) was searched for incidents relevant to the proposed uses of glycerol formate.

Hydrogen peroxide
The IDS was searched on April 26, 2024, using the search terms "hydrogen peroxide" and PC code "000595." The incidents reported did not involve registered antimicrobial products.

Formic acid
The IDS was searched on April 26, 2024, using the search term "formic acid." The incidents reported did not involve registered antimicrobial products.

3. Listed Species of Concern

The uses for glycerol formate, based on the proposed EP label (DuoGuard RTU, Registration No. 1677-EAA), include directions for use for cleaning and disinfecting hard, non-porous surfaces (*e.g.*, counters and tables, toilets, showers, etc.) and for sanitizing soft surfaces (e.g., bedding, blankets, curtains, towels, etc.) at healthcare facilities (e.g., hospitals, medical premises, nursing homes, etc.) using wipes and cloths. While it is possible that spent solution containing PFA and glycerol formate could be discarded down the drain, any potential exposure concentrations are expected to be well below effects levels based on (1) the rapid transformation of glycerol formate and hydrogen peroxide to PFA, (2) the rapid degradation of PFA to formate/formic acid and water, (3) the rapid degradation of glycerol formate to glycerol and formic acid (in the event that any glycerol formate is washed down the drain), (4) the relatively low toxicity profile of glycerol formate, PFA, and its degradates, and (5) the presence of glycerol and formic acid in natural systems in the environment.

Based on the environmental fate characteristics and indoor use pattern, the potential for exposure to aquatic organisms is expected to be negligible. The potential for direct exposure to terrestrial vertebrates and invertebrates from the indoor use of glycerol formate is expected to

be negligible as well. No reasonable expectation of discernible direct or indirect effects to threatened or endangered species or the designated critical habitat for such species is expected from the indoor antimicrobial use of glycerol formate. Therefore, the Agency is making a "no effect" determination under the Endangered Species Act (ESA) based on the negligible expected exposure from the antimicrobial use of glycerol formate and has concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required.

C. Benefits

Glycerol formate is an active ingredient precursor that when combined with hydrogen peroxide (H2O2) will form PFA. According to the registrant, the on-site generated PFA solution presents many benefits over currently available hospital sporicidal disinfectant active ingredients and products. The registrant states: "There are currently two primary active ingredients that achieve sporicidal efficacy against *Clostridium difficile* (*C. diff*) – sodium hypochlorite (NaOCl) and peroxyacetic acid (PAA). The attributes of the PFA solution, ranging from microbiological efficacy performance, to safety, to material compatibility, are favorable when compared to the currently available sporicidal products on the market today."[7] These benefits include health and safety use and handling benefits, environmental benefits, and material compatibility improvements that result in significant costs savings to hospitals.

The performic acid end-use formulation resulting from mixing the proposed product Part A and Part B (in situ) has low eye (Toxicity Category III) and skin irritation (Toxicity Category IV). The signal word on the label is CAUTION. Additionally, there are no occupational or residential bystander risks of concern from the proposed use. Other hospital disinfectants containing active ingredients, such as quaternary ammonium and sodium chlorite, have toxicity profiles that are not as favorable. Some quaternary ammonium products cause eye damage or skin irritation and carry a signal word DANGER. Sodium chlorite labels can also cause eye damage and skin burns and carry a signal word of WARNING or DANGER. Additionally, some of the currently registered hospital disinfectants are corrosive. Sodium chlorite is a strong oxidizer and extended contact with metals may cause discoloration or pitting. Lastly, there are environmental benefits for registering this proposed product. The product is efficacious 60 minutes after mixing, which is more than enough time for hospital staff to conduct various types of room cleaning and disinfection. The registrant also states an additional environmental benefit: "An added benefit to the end user of a task-based use life involves reduced product waste. The reason for this is that product is only produced when it is needed, which restricts the production of a large excess in chemistry and wetted cloths which need to be disposed of or laundered at the end of a shift. Since laundry charges are primarily based on weight, this reduces cost for the customers and reduces waste discharge."[8]

---

[7] Glycerol Formate Overview, dated October 7, 2019. **Author** Eric Ditzel, Ph.D. Ecolab, Inc. (add MRID here if available)

[8] Glycerol Formate Overview, dated October 7, 2019. **Author** Eric Ditzel, Ph.D. Ecolab, Inc. (add MRID here if available)

Disinfection reduces the risk of healthcare-associated infections and having more tools for disinfection helps combat these pathogens. Currently, there are several EPA-registered active ingredients that hospitals use for disinfectants: quaternary ammonium, hypochlorite, accelerated hydrogen peroxide, phenolics, and peracetic acid. According to the registrant: "Glycerol formate is a new active ingredient precursor that will be combined with H2O2 on-site to form PFA. PFA is a short-lived active ingredient that is very efficacious against *C. diff* (MRID 50864539). *C. diff* causes 500,000 hospital acquired infections in the US each year and nearly 30,000 (6%) of those who are infected annually, die within 30 days of initial diagnosis (Fernanda C. Lessa, 2015)".

The registrant has submitted a Glycerol Formate Reduced Risk Rationale which cites other benefits of glycerol formate. This document can be viewed on www.regulations.gov under docket ID#: EPA-HQ-OPP-2020-0120.

V. PUBLIC COMMENTS

On March 27, 2020, the EPA published a Notice of Receipt in the Federal Register of an application for registration of glycerol formate and announced a public comment period of 30 days. No comments were received. The corresponding docket number is EPA-HQ-OPP-2020-0120 on www.regulations.gov.

Public Participation

FIFRA requires public participation in the pesticide registration process for new active ingredients under Section 3(c)(4). The Agency explored opportunities for expanding the openness of the process for new active ingredients and other registration actions. In October 2009, the Agency began implementing a public participation process for certain pesticide registration actions, including registration of products containing a new active ingredient, http://www.epa.gov/pesticides/regulating/public-participation-process.html.

The Agency will consider all public comments received during the 30-day public comment period for this proposal to issue an unconditional registration for the proposed glycerol formate products. During the public comment period, comments should be submitted under Docket ID No. EPA-HQ-OPP-2020-0120 via www.regulations.gov

VI. PROPOSED REGULATORY DECISION

EPA registers a pesticide unconditionally when sufficient data have been submitted and the Agency determines that the proposed uses will not cause unreasonable adverse effects on humans or the environment. When the Agency determines whether the proposed uses will

cause unreasonable adverse effects, it considers the economic, social, and environmental costs and benefits of the use of the pesticide. Under FIFRA, the EPA is charged with balancing risks posed by the use of a pesticide against its benefits. The EPA must determine if the benefits in light of its use outweigh the risks in order for the EPA to register a pesticide.

While there is a potential for human health exposure from the proposed uses of glycerol formate, EPA has determined that the risk associated with potential exposure is low. Additionally, the proposed uses of glycerol formate would provide benefits including health and safety use, handling benefits, microbiological efficacy performance and safety and material compatibility. Because disinfection reduces the risk of healthcare-associated infections, having more tools for disinfection can help combat pathogens. Glycerol formate is mixed with hydrogen peroxide onsite to form PFA. PFA is efficacious against *C. diff* which causes approximately 500,000 hospital acquired infections in the U.S. every year. Weighing these benefits against the low potential for risk, EPA proposes that glycerol formate meets the standard for registration under FIFRA.

A. Rationale

Under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Agency is proposing to unconditionally register a new MUP (EPA Reg. No. 1677-EAL, and EP (919789, EPA Reg. No. 1677-EAA), comprised of a new active ingredient, glycerol formate.

The Agency considers the database complete for assessment of risks to human health and the environment and there are no data gaps. After considering the assessed risk to human health and the environment, the Agency concludes that glycerol formate meets the regulatory standard for registration under FIFRA.

The Agency conducted a health protective Human Health Risk Assessment on PFA. There are no expected dietary exposures to PFA. The registrant did not propose any residential uses; therefore, EPA does not anticipate residential handler exposures.

Based on the use pattern, occupational handler exposures to healthcare workers are anticipated (i.e., amount handled, daily exposure, long-term duration). Exposure will be to PFA, which, according to the proposed labels, remains efficacious for up to approximately one hour from the time the ingredients are combined. It is anticipated that workers will mix and use several batches per day. The inhalation MOE for this use pattern is 110 and not of concern because it is greater than the long-term LOC of 100. In addition, there is the potential for residential bystander (i.e., patient) inhalation exposure to PFA during the application of the proposed product. The patient could be exposed to the product if it is used in occupied rooms. The MOE is 600 which is not of concern because it is greater than the LOC of 100. Therefore, EPA does not anticipate any risks of concern to residential bystanders (i.e., patients) from the proposed use pattern of PFA.

FIFRA prohibits registration of pesticides that generally pose unreasonable adverse effects to the environment. Risks to nontarget terrestrial and aquatic organisms from PFA from the proposed antimicrobial uses of glycerol formate are expected to be negligible. If any environmental exposure to the glycerol formate occurs (e.g., when the spent solution, which initially contains 1% glycerol formate, is disposed of down the drain and potentially be released after wastewater treatment), glycerol formate hydrolyzes rapidly to glycerol and formate/formic acid. Should any glycerol formate be released into the environment, glycerol formate and its degradates have low persistence and are expected to result in limited environmental exposure as well.

The Agency finds low potential for environmental and ecological risks from the proposed uses. Therefore, the Agency is making a "no effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitats for such species based on the expected negligible exposure from the antimicrobial use of glycerol formate. Additionally, the proposed uses of glycerol formate have no potential dietary exposures, low potential for human health risks, and would result in benefits including microbiological efficacy and material compatibility. Because disinfection reduces the risk of healthcare-associated infections, having more tools for disinfection like glycerol formate can help combat pathogens. Therefore, the EPA proposes that using glycerol formate as a disinfectant for, non-porous, non-food contact hard surfaces and as sanitizer for soft surfaces in healthcare settings (e.g., hospitals, medical premises/equipment, and nursing homes) will not cause unreasonable adverse effects on the environment and meets the criteria for unconditional registration under FIFRA Section 3(c)(5).

VII. REFERENCES

All supporting documents can be found in EPA's public docket (EPA-HQ-OPP-2020-0120) at www.regulations.gov.

1. Human Health and Ecological Risk Assessment for the Proposed New Active Ingredient Glycerol Formate as a Non-Food Contact Disinfectant dated March 7, 2024

2. Acute Toxicity Review for DuoGuard RTU Part A and DuoGuard RTU Part B, EPA File Symbol 1677-EAA and 1677-EAT, as combined *in-situ* dated October 30, 2023

3. Glycerol Formate Reduced Risk Rationale dated October 7, 2019, MRID 52369201

4. MUP label (919789, EPA Registration Number 1677-EAL)

5. EP label (DuoGuard RTU, EPA Reg. No. 1677-EAA)