UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

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Subject: Response to Petition to Reconsider and Cancel or Suspend the Registration for Antimicrobial Cupron Enhanced EOS Surface
Your Letters Dated November 2, 2012 and May 28, 2013

This letter constitutes the U.S. Environmental Protection Agency's ("EPA" or "the Agency") response to the Copper Development Association Inc.'s (CDA) (herein referred to as "Petitioner") letter dated November 2, 2012 ("petition"). The petition includes various assertions and questions regarding the registration and efficacy of Antimicrobial Cupron Enhanced EOS Surface (EPA Registration Number 84542-7) ("Cupron/EOS Surface") and asks the Agency to reconsider its registration decision concerning that product, and specifically, to cancel or suspend registration of Cupron/EOS Surface. Additionally, CDA submitted a follow-up letter dated May 28, 2013 that included data that CDA claims demonstrated the inadequate efficacy of Cupron/EOS Surface.

In support of the petition, CDA details technical issues with the Cupron/EOS Surface related to durability, efficacy, resistance, and labeling that CDA contends ultimately pose a "risk to the health of patients, users and other consumers who rely on the 'public health' antimicrobial claims made for the product."

## I. Summary of Agency Response to the Petition

After considering CDA's allegations and the information presented in the petition, as well as the information submitted by Cupron (herein referred to as "Cupron" or "Respondent") in response to the CDA petition (November 5, 2014, January 8, 2015, and February 2, 2015 letters to the Agency from Bergeson & Campbell PC, counsel to Cupron), the EPA has determined that CDA has not presented sufficient information that would support granting the relief requested. Accordingly, EPA is hereby denying the CDA's requests to cancel or suspend the registration of Cupron/EOS Surface.

## II. Legal Framework - FIFRA

Subject to limited exceptions, a pesticide may be distributed or sold in the United States only if it is registered by the EPA. FIFRA § 3(a), 7 U.S.C. § 136a(a). Under FIFRA, the EPA must register a pesticide if, among other things, the pesticide, when used in accordance with widespread and commonly recognized practice, generally will not cause "unreasonable adverse effects on the environment." 7 U.S.C. § 136a(c)(5). Section 2(bb) defines "unreasonable adverse effects on the environment" as, among other things, "any unreasonable risk to man or the

environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide . . . ." 7 U.S.C. § 136(bb)(1).[1]

If the EPA determines at any time that a registered pesticide, including its approved labeling, no longer meets the standard for registration, the EPA may initiate cancellation proceedings. 7 U.S.C. § 136d(b). FIFRA section 6(b) sets forth the requirements for pursuing a cancellation action.

The EPA may also commence proceedings to suspend the registration of a pesticide during the period necessary to complete cancellation proceedings if it determines that an "imminent hazard"[2] exists from the use of the pesticide. 7 U.S.C. § 136d (c). FIFRA also provides the Administrator with emergency suspension authority. Id.

## III. Consideration of Petition and Respondent's Response

In their letter dated November 2, 2012, CDA claims that "fundamental questions regarding the efficacy of the Cupron/EOS Surface, including the long-term durability and antibacterial performance of the product, must be addressed before the Agency should allow the continued marketing and sale of this 'public health' product intended to fight infection-causing bacteria in the healthcare environment and other settings. To do otherwise would pose a risk to the health of patients, users, and other consumers who rely on the 'public health' antibacterial claims made for the product." CDA suggests in its petition that an impregnated copper product, such as the Cupron/EOS Surface product, would have reduced efficacy compared to solid copper alloy products. CDA asserts that for these reasons, "EPA should reconsider and cancel or suspend the registration at this time pending resolution of these critical issues." On May 28, 2013, CDA submitted a follow-up letter that included a study evaluating the efficacy of Cupron/EOS Surface over a two-day test period. CDA claims that the study demonstrates that the Cupron product does not achieve efficacy requirements.

In response to CDA's petition, Cupron provided a detailed history of the registration process for Cupron/EOS Surface (including the pre-application submissions for efficacy protocol reviews) and presented point-by-point responses to each of the issues raised by CDA. Cupron also pointed out that several of the concerns presented by CDA would potentially also apply to CDA's copper alloy products. Finally, Cupron suggests that a more appropriate approach would be for the Agency to utilize the authority set forth in FIFRA Section 3(c)(2)(B) to "collect additional data that can be used to evaluate whether a currently registered product continues to satisfy the standard for registration".

## IV. Detailed Response to Request for Relief under FIFRA

The CDA petition presents eight principal issues in support of its request that EPA reconsider and cancel or suspend its registration decision for the Cupron/EOS Surface product. The discussion that follows, therefore, is organized by issue and includes a summary of each issue and related CDA assertions, a summary of Cupron's response to each issue, and the Agency's position on each issue. Fuller excerpts from the CDA petition and the Cupron response appear in endnotes that are keyed to the various issues to which they relate.



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**Issue One.**

**Petitioner Position:** The Efficacy Test Protocols Were Not Designed to Assess the Performance of a Material That Changes Chemically Over Time [3]

Petitioner asserts that "testing protocols are based on the presumption that the tested material will remain chemically and physically consistent during the useful life of the product" and while the Unified Numbering System (UNS) of metals and alloys "guarantees" the chemistry of copper alloys, "no such guarantee or demonstration has been made for the Cupron/EOS Surface." Petitioner questions the depletion of copper ions from, and the long-term viability and efficacy of, the Cupron product. Petitioner expresses concern about the ability of the existing protocols to demonstrate long-term antimicrobial durability and efficacy, and encourages the Agency to develop "new, more appropriate test protocols."

**Respondent Response:** CDA's Argument that EOS Surface Changes Chemically over Time Is Speculative and without Any Empirical Basis[4]

Respondent claims Petitioner's argument is "wholly speculative" and "not supported by any empirical data demonstrating any alleged changes in the antimicrobial activity of EOS Surface, or even by any quantitative or qualitative modeling of how these alleged changes might occur."

Respondent points out that "CDA's speculation concerning reductions in the efficacy of EOS Surface is not supported by the studies of continuous reduction of bacterial contamination and residual sanitizer activity that support the existing EOS Surface registration, which were conducted according to protocols that EPA reviewed and approved" and that "Cupron and EOS have previously provided information to EPA concerning the uniform distribution of cuprous oxide particles in the polymeric matrix of EOS Surface."

Respondent claims the information submitted to support the Cupron registration demonstrates "the homogenous distribution of copper oxide particles throughout the matrix" and as degradation of EOS Surface occurs over time, "new polymeric material is exposed along with new cuprous oxide particles."

**Agency Position:** The Agency believes copper alloy products are produced to conform to standards (such as UNS, an alloy designation system managed by the Society of Automotive Engineers and American Society for Testing and Materials) but was unable to confirm that UNS makes any "guarantee" of performance specifications or exact composition. Pesticide products must conform to the composition information provided to EPA as part of the registration process for the product, and CDA has not presented compelling evidence/information to convince the Agency that the Cupron/EOS Surface "changes chemically over time." During its review of Cupron/EOS Surface's registration application, EPA evaluated all pertinent data, including supporting efficacy data, and determined the product will perform its intended function without unreasonable adverse effects when used in

accordance with the label directions as specified in Cupron's application for registration. EPA continues to conclude that Cupron met all requirements to demonstrate that its product satisfies the statutory standard for registration and that the efficacy data submitted to support the registration support the labeled efficacy claims. Approved efficacy claims for Cupron/EOS Surface include: "…surface kills greater than 99.9% of Gram negative and Gram positive bacteria within two hours of exposure" and "continues to kill 99% of bacteria even after repeated contamination."

However, EPA agrees with Petitioner that test protocols must be updated, and has already started this process. The Agency will be issuing a new protocol for testing the antimicrobial efficacy of copper-containing surfaces, such as Cupron/EOS Surface. Both CDA and Cupron submitted substantive comments about the September 19, 2014 proposed Protocol for the Evaluation of Bactericidal Activity of Hard, Non-porous Copper/Copper-Alloy Surfaces. CDA also submitted comments to the peer review panel on February 19, 2016. All comments from the public, including CDA's and Cupron's, were provided to the peer review panel for consideration. In developing the new protocol, EPA carefully considered the protocol concerns CDA and Cupron raised in the petition and in their comments about the protocol, particularly those related to efficacy and product durability. Although the Agency is confident that efficacy protocols used to support both the Cupron and CDA product registrations were adequate for that purpose, we appreciate the thoughtful consideration CDA and Cupron gave to the Agency's efforts to update the protocol. Specific to the concern expressed by Petitioner in Issue 1, the robust chemical and physical abrasion process in the updated protocol is designed to challenge the durability of all solid-copper products as well as copper coated/infused products. The Agency is developing a path forward and, at this time, no decision has been made with regard to supplemental testing for existing registered products. More information regarding the updated draft copper protocol can be found online at [ HYPERLINK "http://www.regulations.gov" ] (Docket ID: [ HYPERLINK "https://www.regulations.gov/docket?D=EPA-HQ-OPP-2016-0467" ]) and at [ HYPERLINK "https://www.epa.gov/pesticide-registration/updated-draft-protocol-evaluation-bactericidal-activity-hard-non-porous" ].

**Issue Two.**

**Petitioner Position:** Long-Term Efficacy and Durability of the Cupron/EOS Surface Has Not Been Demonstrated [5]

Petitioner points out that the Cupron/EOS Surface consists of 16 percent copper oxide particles and claims "that copper alloys containing roughly 50 percent or less copper do not demonstrate efficacy under the testing protocols." Petitioner likens the Cupron/EOS Surface product to anti-fouling paint, which must be reapplied periodically to maintain antimicrobial efficacy, claiming the cuprous oxide particles will be depleted with use. Petitioner further questions the long-term stability and durability of the polymeric matrices, claiming they are

susceptible to degradation from "chemical or hydrogen peroxide cleaning systems, as well as from photo-degradation (e.g., from ultraviolet cleaning systems) and/or heat."

**Respondent Response:** Although CDA Alleges that the Long-Term Efficacy of EOS Surface Has Not Been Demonstrated, a Study of Samples of EOS Surface that Were in Actual Service for 18 Months and Were Cleaned with Standard Hospital Disinfectants Found that EOS Surface Remains Fully Efficacious as a Sanitizer[6]

Respondent claims CDA's comparisons of the Cupron/EOS Surface to solid copper alloys and anti-fouling paints is spurious because of differences in material composition. In addition, Respondent presents test data generated from samples of the Cupron/EOS Surface that were in service for 18 months at a health care facility to demonstrate the product remained efficacious throughout that period. Respondent claims these data also contradict CDA's argument that the cuprous oxide in the Cupron/EOS Surface will be degraded or depleted by common cleaning agents since the tested Cupron/EOS Surface was cleaned daily with chemical disinfectants during the 18-month period.

**Agency Position:** Similar to the Agency response to Issue One, above, Petitioner does not present compelling information to support the allegations about the Cupron/EOS Surface product or the adequacy of the EPA evaluation of the Cupron/EOS Surface product for registration. GLP efficacy data (base sanitizer) were submitted by Cupron using Cupron/EOS Surface material that had been in use at a hospital for 18 months. These data were acceptable and confirm the product continued to meet the base sanitizer claim performance standard for *S. aureus* (3-log reduction) over the course of 18 months. Cupron also submitted GLP studies that expanded testing on additional lots/colors of the material, which supported base sanitization claims for both *S. aureus* and *E. aerogenes*. Additionally, there are two peer-reviewed publications that look at the effect of installing Cupron/EOS surfaces in two hospitals (Sifri CD et al., 2016 and Coppin JD et al., 2017), of which the former was conducted over the course of 25 months. These results of these studies demonstrate the Cupron/EOS surfaces remain effective over time.

In regards to the Petitioner's claims of degradation due to chemical cleaning, the 18-month GLP study submitted to the Agency used material that was cleaned daily with a quaternary ammonium compound (quat) product and weekly with oxidizer products. This is similar to a clinical study (Sirfri et al.) in which hospitals used both quat and hypochlorite products on Cupron/EOS surfaces. EPA points out that CDA's concerns regarding incompatibility of copper-based products with chemical treatments used in healthcare facilities (e.g., oxidizers used in hospitals as cleaners/disinfectants may corrode copper) is a concern that is also potentially applicable to CDA's products. Cleaner compatibility was not a component of the efficacy protocols used for supporting registration of any of the copper products (including CDA's products). As such, CDA has not submitted data demonstrating chemical cleaner compatibility for the copper alloy surfaces to



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the Agency. The robust chemical and physical abrasion process in the updated protocol, mentioned in the Agency's response to Issue 1, is designed to address these chemical compatibility concerns.

**Issue Three.**

**Petitioner Position:** The Conditions of the Test Protocols Favor Surfaces That Leach the Active Ingredient [7]

Petitioner alleges that the wet inoculation method utilized in the existing protocol "enhances the efficacy performance of the Cupron/EOS Surface by promoting more rapid leaching of the copper ions from the polymeric substrate and distribution of those ions across the surface." Petitioner questions the performance of the Cupron/EOS Surface "under dry inoculation test conditions."

**Respondent Response:** CDA's Argument that Use of Wet Inoculation in Approved EPA Protocols Favors Copper-Containing Surfaces that Leach the Active Ingredient Is Both Speculative and Contrary to the Actual Test Conditions[8]

Respondent points out that "both [CDA and Cupron/EOS] surfaces are dependent on the availability of copper ions, and there is no basis to suppose that the use of wet inoculation methods would not have a similar effect on the availability of copper ions from a copper alloy surface." Respondent also points out that the "standard test methods allow drying time after the inoculation step, so these test methods also reflect the antibacterial efficacy of EOS Surface in dry conditions."

**Agency Position:** The Agency believes that both Cupron and CDA copper products would be equally impacted by increased humidity, and as such, efficacy would not be enhanced in one product over the other. With regard to the performance of products under varying environmental conditions such as humidity, testing of a product should occur under the intended use conditions (e.g., climate-controlled space in US hospitals). Additionally, the updated study protocol indicates that the temperature and humidity should be recorded and included in the final study report for the carrier storage and two-hour exposure period.

**Issue Four.**

**Petitioner Position:** The Potential for Formation of Resistant Organisms Should Be Examined[9]

Petitioner expresses concern that the Cupron/EOS Surface "may serve as havens for bacteria" and that the product may increase "the potential for development of microbial resistance [to copper]."

**Respondent Response:** Although CDA Alleges that Resistant Organisms May Develop Because EOS Surface Only Delivers a Sub-Lethal Dose, Actual Research Found



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No Evidence of Development of Any Resistant Subpopulation Even at a Lower Dose[10]

Respondent points to a previously published study in a peer reviewed journal that assessed formation of copper-resistant subpopulations after repeated exposure to cuprous oxide impregnated in a polymeric matrix at a lower concentration. This study found no evidence of development of any resistant subpopulation even after repeated bacterial insults.

**Agency Position:** EPA recognizes that development of resistance may be a potential concern after repeated exposure to antimicrobial copper. As pointed out in the article cited by Cupron[11], there are examples in the literature of bacteria with decreased sensitivity to copper due to long term (months to years) exposure to copper. However, there are a number of considerations that highlight the relatively low risk of development of resistance to copper, including: 1) copper tolerant microbes are rare despite the prevalence of copper over thousands of years; 2) the level of resistance to copper (10-fold more resistant) in comparison to reported resistance to antibiotics (2200-fold more resistant) highlights the difference between resistance to copper and resistance to antibiotics as it relates to public health; and 3) the bactericidal mechanism of copper is relatively nonspecific, resulting in damage to many components of the bacterial cell in contrast with mechanisms for antibiotic bactericidal activity which often target a single component of the cell and, as such, may be a reason resistance to antibiotics develops easier. Finally, while the Agency expects there to be relatively low risk of copper-resistance development, since microorganisms would be exposed to copper from any copper product (including CDA's products), CDA's concerns regarding the development of copper-resistant organisms would be applicable to CDA's products as well as Cupron's product.

**Issue Five.**

**Petitioner Position:** How Is the Product Chemistry Guaranteed?[12]

Petitioner questions how "a uniform concentration of copper ions at the surface level" is guaranteed across manufacturing lots. Petitioner also suggests that "downstream processing activities" (e.g., buffing, grinding, etc.) "would be expected to generate heat" that could "cause the polymer to spread and coat the cuprous oxide, rendering it unavailable for contact with bacteria." Petitioner cites and links to an "EOS fabrication manual" which mentions abrasion finishing techniques that could alter the finish and potentially affect efficacy.

**Respondent Response:** Although CDA Questions the Consistency of Product Chemistry across Different Manufacturing Lots, Product Stewardship Studies Demonstrate Consistent Efficacy as a Sanitizer in Three Independent Manufacturing Lots and Multiple Replicates from Each Lot[13]

Respondent points out that the "EOS fabrication manual" cited to by Petitioner "is not the correct fabrication manual for the registered EOS Surface product" and that Petitioner presents no information or data that would establish any basis for the concerns about inconsistency of product chemistry for the Cupron/EOS Surface across differing manufacturing lots. Respondent claims the finishing step does not alter the "uniform distribution of the pesticidal active ingredient throughout the polymeric matrix of the entire product" and that heat generated during the finishing "will have no effect on the particles of active ingredient impregnated in the polymeric matrix."

**Agency Position:** As Respondent mentions in their response, the manual cited by the Petitioner is for a different product (i.e., not the registered Cupron/EOS Surface). As mentioned in the Agency Position on Issue Two, Cupron submitted acceptable GLP efficacy data using additional lots/colors of the Cupron/EOS Surface material and confirming efficacy after use at a hospital for 18 months. These data continue to support the base sanitizer claim. While it is the responsibility of the registrant to ensure consistency across manufacturing lots, EPA has no information/data that calls into question the production process and composition information provided to, and approved by, the Agency during the registration of Cupron/EOS Surface.

**Issue Six.**

**Petitioner Position:** <u>There Is a Disconnect Between the Directions for Use and the Functioning of the Product[14]</u>

Petitioner expresses concern that having the active ingredient embedded in a polymeric substrate effectively 'coats' the product (coating the product is prohibited in the directions for use), thereby making copper ions unavailable over time.

**Respondent Response:** <u>CDA's Allegation that There Is a Disconnect between the Directions for Use and Functioning of EOS Surface Incorrectly Conflates the Issue of a Barrier if the User Coats the Product and the Availability of Copper from the [uncoated] Polymeric Matrix[15]</u>

Respondent points to their 18-month efficacy data to contradict Petitioner's argument and support Respondent's claims that coating the product ("introduction by the user of a physical barrier to availability of the active ingredient") is unrelated to "the potential availability of active ingredient that is embedded in the polymeric matrix."

**Agency Position:** EPA considered the issues raised in the petition, and re-reviewed the labeling for Cupron/EOS Surface. Coating the product continues to be prohibited on the label. EPA does not consider the impregnation of the active ingredient into the polymeric matrix to be equivalent to "coating" the product. EPA found no

deficiencies or inconsistencies in this regard that call into question its original decision to register the pesticide product.

**Issue Seven.**

**Petitioner Position:** The Cleaning Instructions Are Contrary to the Required Claim Language[16]

Petitioner claims cleaning instructions (to avoid certain chemicals) on the Cupron/EOS website contradict the directions for use on the product label.

Petitioner points to an article, to which the Cupron/EOS website links, which states that the countertop "essentially cleans itself" (contrary to the "concept that the product is a supplement to, not a substitute for, routine cleaning procedures").

**Respondent Response:** CDA Incorrectly Cites Cleaning Instructions on the Cupron Website that Concern a Different Product, and Also Cites Statements in a Newspaper Article Concerning EOS Surface that Was Not Written by Cupron[17]

Respondent argues that Petitioner's assertions are "misleading," and states that the "cleaning instructions cited by CDA are for an entirely different EOS product line," pointing to "the correct cleaning instructions for the registered Cupron/EOS product that is the subject of the CDA petition" on a different website.

While Respondent argues that the newspaper article which refers to EOS Surface as an item "that essentially cleans itself" was not written by Cupron or EOS, Respondent states that they have removed the link to the article from their website.

**Agency Position:** EPA considered the issues raised in the petition, and re-reviewed the labeling for Cupron/EOS Surface as well as the language on the various websites mentioned by both CDA and Cupron. The cleaning instructions cited by CDA are for a different (residential) product, and a check of the website shows that the article entitled "Self-cleaning countertop?" has been removed. EPA found no deficiencies or inconsistencies in this regard that call into question its original decision to register the pesticide product.

**Issue Eight.**

**Petitioner Position:** The Registration Should Be Specific to Countertops[18]

Petitioner argues product performance may differ based on the form of the material since different processing may affect the product chemistry. Petitioner suggests the Cupron/EOS Surface registration be limited to just countertops since efficacy in other forms (e.g., tubular) were not evaluated.

**Respondent Response:** CDA's Argument that the Registration Should Be Specific to Countertops Has No Empirical or Theoretical Basis, and Is Equally Applicable to Copper Alloy Surfaces[19]

Respondent states "[a]ll EOS Surface products…, regardless of form factor, must conform to the composition information provided to EPA as part of the registration process for the product" and that the production process submitted to satisfy requirements for registration show "that particles of cuprous oxide are uniformly distributed throughout the entire polymeric matrix." Respondent also argues that if "there is some valid reason to require separate testing for any other form factor, it is likely that the rationale for such testing would apply with equal force to copper alloy products." Respondent further states that "any data needs based on newly identified questions can be appropriately addressed through the DCI process, and are not a proper basis for a petition to cancel."

**Agency Position:** Like other pesticide products, Cupron/EOS Surface products must conform to the composition information provided to EPA as part of the registration process for the product (regardless of form factor). Therefore, there should be no difference in the uniform distribution of cuprous oxide within the Cupron/EOS Surface when shaped or formed for different end uses. Moreover, as Respondent correctly notes, an argument for requiring separate testing of all shapes would appear to apply equally to all copper alloy shaped surfaces, not just those incorporating Cupron/EOS Surface. Finally, we have no information/data that calls into question the production process and composition information provided to the Agency during the registration of Cupron/EOS Surface, nor does CDA provide compelling evidence that different forms of Cupron/EOS Surface are inadequately covered by the product performance data supporting the registration.

In regards to the study submitted on May 28, 2013 by CDA, the submitted data were not generated under Good Laboratory Practices and the source/previous handling of the test material were unknown to the Agency. Despite not meeting standards sufficient for Agency review, a limited appraisal of the study revealed problematic inconsistencies. For example, in some tests, the Cupron product performed, while in others, it did not. This ambiguity and variability in results and lack of detail in how the studies were conducted prevents the Agency from agreeing with CDA's assertion that the data submitted by CDA demonstrate that the Cupron/EOS Surface product does not meet efficacy standards. Thus, the Agency continues to rely on its review of supporting efficacy data generated under Good Laboratory Practices submitted in support of Cupron/EOS Surface's registration application.

## V. Conclusion

As with CDA's copper alloy products, Cupron/EOS Surface is only a supplemental treatment and is not allowed as a stand-alone product where infection control is needed; users must continue to follow all current infection control practices including those practices related to cleaning and disinfection of environmental surfaces. Even assuming that CDA is correct that the Cupron product provides reduced efficacy compared to solid copper alloy products, EPA has

determined that CDA failed to show that the Cupron product does not meet the standard for registration (i.e., pose an unreasonable risk to man or the environment or, as posited by CDA, "pose a risk to the health of patients, users, and other consumers who rely on the 'public health' antibacterial claims made for the product"). Thus, EPA does not find that use of the product would cause unreasonable adverse effects on human health or the environment.

For the reasons set forth above, the Agency concludes that the petitioner has not carried their burden of demonstrating the appropriateness of the requested relief. Therefore, following consideration of the Petition, the Response, and the supporting materials, the EPA denies the request to cancel or suspend the Cupron/EOS Surface registration. If you have any questions, please contact John Hebert at (703) 308-6249 or via e-mail at [ HYPERLINK "mailto:hebert.john@epa.gov" ].

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Richard P. Keigwin, Jr.
Director, Office of Pesticide Programs

cc: Lynn Bergeson, Bergeson & Campbell PC, authorized representative of Cupron, Inc.
Joe Greene, Kelley Drye, counsel for CDA

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[1] The definition of the term in FIFRA section 2(bb) also includes "(2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 346a of Title 21" (section 408 of the Federal Food, Drug, and Cosmetic Act). However, the petition did not include any assertions regarding a human dietary risk from residues from use of Copper/EOS Surfaces in or on food.

[2] Section 2(l) of FIFRA defines imminent hazard as "a situation which exists when the continued use of a pesticide during the time required for cancellation proceeding would be likely to result in unreasonable adverse effects on the environment or will involve unreasonable hazard to the survival of a species declared endangered by the Secretary of the Interior under Public Law 91–135."

[3] Issue One Text from Petition: Unlike a sanitizing spray or similar antimicrobial treatment, which have an immediate but short-term sanitizing or disinfecting effect, an antimicrobial solid surface is intended to continually reduce bacterial load during the useful life of the product, which can be a decade or longer (such as a countertop in a hospital or home). Accordingly, to demonstrate efficacy for solid metal materials, the three testing protocols are based on the presumption that the tested material will remain chemically and physically consistent during the useful life of the product. The consistency of copper alloys in this regard has been demonstrated for decades under the ASTM/UNS program, which guarantees the chemistry of the alloy. No such guarantee or demonstration has been made for the Cupron/EOS Surface. Accordingly, the antibacterial performance of the Cupron/EOS Surface over the two- and 24-hour testing protocols does not support efficacy over a longer period of time, and, therefore, does not support the efficacy of a product with an expected useful life of many years. Long-term efficacy of the product must be demonstrated through the development and use of new, more appropriate test protocols.
Question: How fast are the active copper ions depleted from the cuprous oxide on the surface?
Question: What is the long-term viability and efficacy of the cuprous oxide?
Question: What test protocol may be used to demonstrate long-term antimicrobial durability and efficacy of the product?

[4] Issue One Text from Response: CDA argues that EOS Surface "changes chemically over time," and that the active copper ions will be "depleted" over the time that the material is in service. This argument is wholly speculative. This conjecture by CDA is not supported by any empirical data demonstrating any alleged changes in the antimicrobial



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activity of EOS Surface, or even by any quantitative or qualitative modeling of how these alleged changes might occur.

CDA's speculation concerning reductions in the efficacy of EOS Surface is not supported by the studies of continuous reduction of bacterial contamination and residual sanitizer activity that support the existing EOS Surface registration, which were conducted according to protocols that EPA reviewed and approved. Moreover, this speculation is also expressly contradicted by new data on the continued antimicrobial activity of samples of EOS Surface that have been in actual service for 18 months, which is discussed below.

In responding to these allegations, it is helpful to review basic information on the composition of EOS Surface and the active antibacterial agent that is incorporated in the product. The active ingredient in EOS Surface is cuprous oxide, also known as copper (I) oxide, which is a principal oxide of elemental copper. Cuprous oxide is a latticed structure mineral that can only be dissolved in ammonium hydroxide, aqueous ammonia and its salts, and concentrated acids. Cuprous oxide has a boiling point of 1,800°C and a melting point of 1,235°C. The mode of antibacterial activity for cuprous oxide (and also for other copper-containing compounds) involves localized oxidation of the bacterial outer cell membrane. This oxidation process generates free radicals, and directly affects a range of cellular targets within the bacterial cell.

Cupron and EOS have previously provided information to EPA concerning the uniform distribution of cuprous oxide particles in the polymeric matrix of EOS Surface. The submitted information included SEM imaging of a cross section of the EOS Surface matrix clearly demonstrating the homogenous distribution of copper oxide particles throughout the matrix. As degradation of EOS Surface occurs over time, new polymeric material is exposed along with new cuprous oxide particles. There is no portion of the polymeric matrix of EOS Surface that can be exposed during gradual degradation in which cuprous oxide particles will not be exposed as well.

[5] Issue Two Text from Petition: The Cupron/EOS Surface consists of copper oxide particles (16 percent cuprous oxide by weight, or approximately 14 percent copper) that are impregnated into a polymeric substrate from which copper ions leach. The copper oxide particles, based on the densities of the active and inert ingredients, comprise approximately less than three percent of the volume and surface area of the product. Based on a long history of testing, CDA is aware that copper alloys containing roughly 50 percent or less copper do not demonstrate efficacy under the testing protocols.

Polymeric matrices, by their nature, degrade and do not have the inherent structural or mechanical stability of solid copper alloys. Degradation of the polymer may result from chemical or hydrogen peroxide cleaning systems, as well as from photo-degradation (e.g., from ultraviolet cleaning systems) and/or heat. The long-term stability and durability of the polymeric counter tops has not been demonstrated.

Most importantly, the antimicrobial performance of the Cupron/EOS Surface is based on the leaching of copper ions from the material. These ions leach out of the surface and eventually will be depleted. While rapid copper ion release may account for efficacy in the short term (such as under the two- and 24-hour testing protocols), the leaching action suggests a finite limit to the active ingredient contained in the polymeric substrate. Further, common cleaning agents may deplete the active ingredient on the surface.

Upon depletion, due to the encapsulation of remaining copper oxide particles in the polymeric substrate, no active ingredient will be available to take the place of the depleted particles at the surface – unless a significant portion of the polymer is worn away (which, if so, raises questions about the durability of the surface). Accordingly, long-term efficacy of the product is questionable and has not been demonstrated.

Question: How, if at all, do the cuprous oxide particles embedded in the polymer matrix get to the surface, particularly after the surface particles are depleted of copper ions?

Question: Are the cuprous oxide ions active over the entire useful life of the product? How is this demonstrated, if at all?

The phenomenon is similar to (cuprous oxide-containing) anti-fouling paint, which must be reapplied periodically as the copper ions are released and the antimicrobial efficacy of the paint depleted. In contrast, copper alloys, containing 60-99.9% copper, do not deplete and there is a near-infinite supply of copper available throughout the alloy matrix.

[6] Issue Two Text from Response: CDA alleges that the long-term efficacy and durability of EOS Surface has not been demonstrated. The key premise upon which CDA predicates its argument is that there is a finite supply of cuprous oxide in the polymeric matrix of EOS Surface that will be depleted while the material is in service, thereby resulting in reduction of the antimicrobial efficacy of the product. As noted above, this premise is not supported by any empirical data or by any modeling of the availability of cuprous oxide in the polymeric matrix. CDA argues that copper alloys containing 50 percent or less copper are not efficacious, but these materials are radically different in composition from EOS Surface, and no scientifically valid inference can be drawn from this comparison. CDA's comparison of EOS Surface to anti-fouling paint containing copper biocides is equally spurious.

In contrast to these speculative allegations unsupported by any data, Cupron and EOS have sponsored research in which an independent laboratory tested the continued antibacterial activity of samples of EOS Surface that were in actual service for 18 months at a hospital intensive care unit. Cupron and EOS decided to conduct this additional research as part of their ongoing product stewardship, prior to the time they were informed of the CDA petition. During the period that the tested samples were in service, they were cleaned on a daily basis with disinfectants approved for use in that facility. A GLP compliant study conducted for Cupron and EOS found that multiple replicates of EOS Surface removed from actual service remained efficacious as a sanitizer, controlling Staphylococcus aureus at a percent reduction exceeding 99.9%. Thus, the supposition by CDA that EOS Surface will lose efficacy due to depletion of cuprous oxide from its surface is contradicted by test data from samples of EOS Surface that were in actual service at a health care facility for an 18-month period.

Similarly, the argument that the cuprous oxide in EOS Surface will be degraded or depleted by common cleaning agents is contradicted by the fact that the tested samples were cleaned on a daily basis using EPA approved disinfectants during the same 18-month period. In any case, any purported concern about the long-term durability of EOS Surface is of dubious relevance here unless it would affect the antimicrobial efficacy of the material. Since the active ingredient is distributed uniformly throughout the polymeric matrix, there is no reason to suppose that wear or abrasion would reduce efficacy. In addition, the previously submitted study of the residual self-sanitizing activity of EOS Surface expressly addressed the issue of wear and abrasion.

In the face of actual scientific evidence, conjecture by CDA that EOS Surface will become ineffective over time must be rejected. Certainly there is no valid basis for EPA to consider cancellation of the product, even if EPA ultimately decides it would be appropriate to issue a DCI for additional supporting data.

[7] Issue Three Text from Petition: As observed in commercial silver-containing coatings (Michels et al., *Letters in Applied M*icrobiology 49 (2009) 191–195), the efficacy of surface materials impregnated with antimicrobial additives, is highly dependent on the presence of moisture. At high levels of humidity, these products demonstrate some level of efficacy, while little to no efficacy is seen at normal or low levels of humidity. The wet inoculation method utilized in the solid surface testing protocols likely enhances the efficacy performance of the Cupron/EOS Surface by promoting more rapid leaching of the copper ions from the polymeric substrate and distribution of those ions across the surface. Under dry conditions, such as those involving the transfer of bacteria from contaminated hands, which are more likely to be experienced in hospital settings or the home, the copper ions would not be expected to be transported across the product surface as readily, resulting in reduced efficacy. [In contrast, the performance of copper alloys is not dependent on the transport of copper ions across the surface, as the high percentage of copper in the alloy results in direct bacterial contact with the copper.]

Question: How does the Cupron/EOS Surface, which is dependent on the spreading of copper ions across the surface, perform under dry inoculation test conditions?

Question: Will the copper ions be released in the typical dry environment?

Question: Under typical (dry) environmental conditions, how do the copper ions (which represent approximately three percent of the product surface area) impact the remaining 97 percent of the surface area that is comprised of inert ingredients?

[8] Issue Three Text from Response: CDA also argues that the standard EPA protocols for testing sanitizers are not appropriate for durable antimicrobial surfaces, because these protocols favor those surfaces that leach the active ingredient. The implicit premise of this argument is that EOS Surface leaches the active ingredient, while copper alloy surfaces do not. This is a dubious premise, because the antimicrobial properties activity of both surfaces are dependent on the availability of copper ions, and there is no basis to suppose that the use of wet inoculation methods would not have a similar effect on the availability of copper ions from a copper alloy surface. In any case, the standard test methods allow drying time after the inoculation step, so these test methods also reflect the antibacterial efficacy of EOS Surface in dry conditions.

[9] Issue Four Text from Petition: As noted above, the relatively small amount of active ingredient – approximately less than three percent by volume and surface area – in the Cupron/EOS Surface means that large areas of the product may serve as havens for bacteria. While some bacteria would encounter the copper ions leached from the Cupron/EOS Surface – particularly, as discussed above, when the ions are spread across the surface during the wet inoculation method used in the testing protocols – many bacteria would be expected to be present in the approximately 97 percent of the surface that is non-copper. Organisms that reside on surfaces with lower concentrations of copper ions, or none at all, may receive a sub-lethal dose. Prolonged exposure to a sub-lethal dose of copper ions increases the potential for development of microbial resistance. Depletion of copper ions over time, as discussed above, is likely to exacerbate this potential risk.

Question: Has the issue of the potential formation of copper-resistant organisms been examined? How can the registrant guarantee that resistance will not develop given the potential for delivery of sub-lethal doses of copper ions as the ions are depleted and/or bacteria reside on the non-copper polymer portion of the surface?

[10] Issue Four Text from Response: CDA asserts that use of EOS Surface may promote resistant organisms, based on a supposition that exposed organisms will receive a sub-lethal dose, thereby promoting development of microbial resistance. Like other speculative inferences by CDA, this is contradicted by data. Cupron previously published a study in a peer reviewed journal that assessed formation of resistant subpopulations after repeated exposure to the same active ingredient impregnated in a polymeric matrix at a lower concentration. This study found no evidence of development of any resistant subpopulation even after repeated bacterial insults.

[11] Borkow G, Okon-Levy N, Gabbay J. 2010. Copper Oxide Impregnated Wound Dressing: Biocidal and Safety Studies. WOUNDS 22(12):301- 310.

[12] Issue Five Text from Petition: While Cupron/EOS indicate that the manufacturing process results in the uniform distribution of the active ingredient throughout the polymeric substrate, it is unclear how this guarantees a uniform concentration of copper ions at the surface level. How can consistent concentrations of cuprous oxide at the surface be guaranteed by the manufacturer, particularly across different manufacturing lots?

Moreover, downstream processing activities – such as buffing or polishing to achieve a semi-gloss finish, cutting, grinding, or forming into different shapes – would be expected to generate heat that could affect the polymeric substrate. This could cause the polymer to spread and coat the cuprous oxide, rendering it unavailable for contact with bacteria.

The EOS "fabrication manual" (available at a link at http://eos-surfaces.com/eos/commercial/) indicates that "the finish delivered to the fabricator is a 'factory finish,' and not a final finish. EOS Fabrication Manual at 102. The fabricator is required to use 'standard solid surface finishing steps' to create the desired finish." One option is a semi-gloss finish. CDA is concerned that the inherent heat associated with abrasion finishing techniques could alter the finish from the one that EPA evaluated in the tests submitted; and that there are no controls over how a surface finish (and hence efficacy) can be affected by an installer/fabricator. In fact, EOS expressly disclaims responsibility for the finish in its product warranty: "EOS™ Surfaces LLC does not warranty finishes, it is the responsibility of the fabricator to provide a proper finish to the consumer." EOS Fabrication Manual at 77. These issues and concerns do not exist with copper alloys.

Question: How does the registrant guarantee the batch-to-batch consistency of the Cupron/EOS Surface?

Question: How is chemistry certified? Under what universally-accepted standard?

Question: What assurance is there that the chemistry and performance of the Cupron/EOS Surface does not change throughout the manufacturing and fabrication processes? After downstream processing and finishing?

[13] Issue Five Text from Response: CDA questions the consistency of product chemistry for EOS Surface across differing manufacturing lots, and the effect of the fabrication step on the efficacy of the finished product. Like its other allegations, CDA has no information or data that would establish any basis for these concerns.

With respect to product variability over differing manufacturing lots, Cupron and EOS have generated actual data as part of product stewardship that shows that differing lots of EOS Surface are equally efficacious. GLP compliant studies conducted for Cupron and EOS at an independent laboratory evaluated the antimicrobial efficacy of multiple replicates of three manufacturing lots of EOS Surface (beige) and three manufacturing lots of EOS Surface (grey). In each instance, the study demonstrated that every replicate for every manufacturing lot was an effective sanitizer, with a control level exceeding 99.9% for *Staphylococcus aureus* and *Enterobacter aerogenes*.

With respect to the allegation by CDA that the product preparation done by fabricators may affect the efficacy of the finished EOS Surface, there is no basis for this supposition. The finishing step does not and cannot alter the uniform distribution of the pesticidal active ingredient throughout the polymeric matrix of the entire product. Moreover, given the high melting point of cuprous oxide, any heat generated during the finishing process will have no effect on the particles of active ingredient impregnated in the polymeric matrix.

CDA also purports to cite the "EOS fabrication manual." The document that is linked in the CDA submission, however, is not the correct fabrication manual for the registered EOS Surface product.

[14] Issue Six Text from Petition: The Directions for Use state that the product must not be "coated" in any way. The purpose of this instruction is to prevent the formation of a barrier between the active ingredient and bacteria. Yet with the exception of a finite amount of cuprous oxide on the surface, the remaining active ingredient is encapsulated by the "non-porous" polymeric substrate and unavailable to replenish the cuprous oxide that will be depleted of copper ions over time (as discussed above). The EOS/Cupron website makes this point clear, stating that "[t]hese copper oxide-infused polymers are embedded into the material." ([ HYPERLINK "http://eos-surfaces.com/cupron/" ])

Question: How can the copper ions be available if the cuprous oxide is embedded in the polymeric substrate, particularly after the active ingredient is depleted at the surface?

[15] Issue Six Text from Response: CDA asserts that there is some sort of "disconnect" between the directions for use that state that the product should not be coated by the user and the intrinsic nature of EOS Surface. Frankly, Cupron and EOS find this argument to be incoherent. There is no reason to suggest that the introduction by the user of a physical barrier to availability of the active ingredient is related to the potential availability of active ingredient that is embedded in the polymeric matrix. At best, this argument is just a variant on the general notion that copper ions will be depleted and the efficacy will decline over time, an argument that is contradicted by actual data.

[16] Issue Seven Text from Petition: The product label includes mandated language, qualifying the basic antibacterial claims, that instructs users to "continue to follow all current infection control practices, including those practices related to cleaning and disinfection of environmental surfaces." Further, the Directions for Use state that "[c]leaning agents typically used for traditional touching surfaces are permissible; the appropriate cleaning agent depends on the type of soiling and the measure of sanitization required." However, the Cupron/EOS website states that "strong acidic cleaners" should not be used on the product. (http://eos-surfaces.com/eos/residential/product-care/) A number of common hospital cleaning agents, as well as those used in the home, are acidic, some of which are highly so (such as those containing acetic acid and citric acid).

Question/Issue: What effect will cleaners, acids, solvents, etc. have on the cuprous oxide? The Directions for Use must be amended to comport with the cleaning instructions that EOS/Cupron post on their website.

In addition, the EOS/Cupron website includes an article entitled "Self-cleaning countertop?" The article further states that the countertop "essentially cleans itself." These statements are in clear contradiction to the mandated label language noted above, and the fundamental stewardship concept that the product is a supplement to, not a substitute for, routine cleaning procedures.

[17] Issue Seven Text from Response: CDA also argues that the cleaning instructions on the Cupron website are contrary to label directions, and that an article referenced on the Cupron website makes inappropriate claims. Before addressing these allegations, it should be pointed out that, even if there was any substance to them (which there is not), such allegations would have no discernible relevance to a petition to cancel or to suspend the registration for EOS Surface. In any case, like so many other assertions by CDA, these assertions are misleading.

The cleaning instructions cited by CDA are for an entirely different EOS product line, as should have been apparent from the word "residential" that is included in the web URL referenced by CDA. The correct cleaning instructions for the registered Cupron/EOS product that is the subject of the CDA petition are included in a different website (www.eoscu.com) that was expressly built for that product, and all materials in that website are entirely consistent with the approved registration for that product.

CDA also refers to an article referenced on the EOS/Cupron website that refers to EOS Surface as an item "that essentially cleans itself." This colloquial description of the nature of the product appears in a newspaper article published in the Richmond Times Dispatch, and it is neither fair nor appropriate to attribute statements made in such a press account to Cupron or to EOS. Nevertheless, to avoid any incorrect impression, Cupron and EOS have decided to remove the link to this newspaper article from their website.

[18] Issue Eight Text from Petition: If the Cupron/EOS Surface registration is to continue, it should only be approved for countertops. From the available information, it appears that only slab material used to make EOS Surface countertops was evaluated; there is no information regarding manufacture of the product into tubular and other forms. To make other forms entails different processing stages that can affect the chemistry of the final product. This is unlike copper alloys, which must meet ASTM/UNS specifications in any form in which the alloy is produced. In contrast, the polymeric base of the Cupron/EOS Surface can be altered through different processing stages. Accordingly, the performance of the material in slab/countertop form is not representative or a guarantee of performance in other forms (such as tubular railings, grab bars, hand rails, bed rails, cart handles, towel bars, exercise equipment, etc.). For this reason, the approved list of applications on the current label is overbroad and unsubstantiated.

In short, if allowed, the Cupron/EOS registration should be a product registration, and not a broad material registration, unless there is a universally (industry) agreed upon standard for certifying content, and unless the content can be assured not to change over the lifetime of the material. Unlike copper alloys that do not physically change by fabrication with the base metal, there is no evidence that all of the applications listed on the EOS registration are capable of being manufactured from the Cupron/EOS polymer matrix, nor that the processing requirements to manufacture these items would not alter the nature of the matrix and antimicrobial efficacy of the product.

[19] Issue Eight Text from Response: CDA argues that the registration for EOS Surface should be limited to countertops because there is no assurance that the composition of the material will not vary depending on the form

in which it is sold, and because there may be differences in antimicrobial performance based on the form of the material. During the registration process, Cupron and EOS provided to EPA a description of the production process for EOS Surface, which assures that particles of cuprous oxide are uniformly distributed throughout the entire polymeric matrix. This uniform composition is not altered when the polymeric matrix is shaped or formed for different end uses, because the amenable nature of thermoplastic polymers allows the material to be worked easily into a range of form factors. CDA argues that copper alloy products are different from the EOS Surface because they must all meet general industry specifications, but this argument has no foundation. All EOS Surface products that are sold, regardless of form factor, must conform to the composition information provided to EPA as part of the registration process for the product.

There is no plausible reason to suppose that the antimicrobial efficacy of a polymeric matrix of uniform composition would differ depending on the form factor. Testing every form factor that is sold for antibacterial efficacy would be scientifically unjustified, and such a policy would require significant expenditures on the development and implementation of new testing protocols. If EPA were to determine that there is some valid reason to require separate testing for any other form factor, it is likely that the rationale for such testing would apply with equal force to copper alloy products. In any event, any data needs based on newly identified questions can be appropriately addressed through the DCI process, and are not a proper basis for a petition to cancel.



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