# Safety of Using Copper Oxide in Medical Devices and Consumer Products

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**Abstract:** Copper has two key properties that make it an active ingredient in the medical devices currently being developed. First, copper is an essential trace element needed by humans, which plays a key role in many physiological processes in different tissues. For example, copper has been shown to be involved in angiogenesis and in wound healing. Second, copper has very potent antibacterial, antifungal, antiviral, and acaricidal properties.

Recently, a novel technology has been developed that introduces copper oxide particles into polymeric materials, where they serve as a slow release source of copper ions. For example, by using this technology, copper oxide containing wound dressings that enhance wound healing; copper oxide containing antiviral respiratory masks that reduce the risk of infection; socks that protect from athlete's foot, and acaricidal bedding products that kill dust mites, have been developed.

While copper oxide is used as the source of copper in mineral and vitamin supplements and is considered safe, its use in medical devices, as well as in industrial and consumer products, is novel. The current manuscript reviews the safety aspects of the use of copper oxide in products that come in contact with open and closed skin.

Copper oxide products have been tested in 9 clinical trials and in several non-clinical studies and have been found to be non-irritating, non-sensitizing, and safe to use, with not even one adverse reaction recorded, both when in contact with intact and broken skin. This is in accordance with the extremely low risk of adverse reactions attributed to dermal exposure to copper.

**Keywords:** Biocide, clinical trials, copper oxide, medical devices, safety, skin.

## COPPER IS AN ESSENTIAL TRACE ELEMENT FOR HUMANS

Copper is an essential trace element involved in numerous human physiological and metabolic processes. Copper is incorporated into over 30 proteins and enzymes that carry out fundamental biological functions such as hemoglobin formation, drug/xenobiotic metabolism, carbohydrate metabolism, catecholamine biosynthesis, the cross-linking of collagen, elastin, and hair keratin, and the antioxidant defense mechanism [1-4].

A healthy, 70-kg, human adult has about 110 mg of copper, with about 50% being present in bones and muscles, 15% in skin, 15% in bone marrow, 10% in the liver and 8% in the brain [5]. The National Academy of Sciences Committee established the U.S. Recommended Daily Allowance of 0.9 mg of copper for normal adults [6]. Copper is ubiquitous and naturally occurs in many food sources such as nuts, organ meats, and grains. The uptake, control of the copper levels and its distribution in different tissues are a very precise orchestrated process [5,7].

It was hypothesized that in some pathogenic conditions due to ischemia, such as in diabetic and chronic venous ulcers or pressure sores, the reduced copper levels in the relevant tissues are partially responsible for the pathological condition [8]. It was further hypothesized that introducing copper into wound dressings would not only reduce the risk of wound and dressing contamination (see below Copper as a Biocide), but, more importantly, would stimulate faster wound repair directly [8]. This would be done by the release of copper from the wound dressings directly into the wound site inducing angiogenesis and skin regeneration [8]. This hypothesis was proven in a diabetic mouse model [9]. Furthermore, it was also hypothesized that copper ions released from copper oxide impregnated socks would improve the well-being of the skin of diabetic patients by inducing angiogenesis and expression and stabilization of extracellular skin proteins, in addition to their biocidal effect of reducing the risk of fungal and bacterial infection of the diabetic foot [10]. Thus, the use of copper impregnated socks may be regarded as a preventive modality.

## COPPER AS A BIOCIDE

Copper has been used as a biocide for centuries [11]. In ancient Egypt and Greece copper was used to sterilize water, treat wounds and pulmonary diseases. During the Roman Empire, copper cooking utensils were used to prevent the spread of diseases. The Aztecs used copper oxide and malachite for treating skin conditions. In India, Hindu devotees for centuries drink water that is stored in copper utensils as it keeps the water sparkling clean. Early American pioneers moving west across the American continent put copper coins in large wooden water casks to provide safe drinking water

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for their long journey. By the 18th century, copper had come into wide clinical use in the Western world for the treatment of lung and mental disorders. In the 19th century copper sulphate, a soluble form of copper, became the fungicide of choice in the U.S. and France for spraying grapes and vines to fight mildew. In the Second World War, Japanese soldiers put pieces of copper in their water bottles to help prevent dysentery.

The fungicidal, antibacterial, and antiviral properties of copper have been demonstrated in many controlled laboratory studies and are very well documented (for a review see [12,13]). Copper exerts its toxicity to microorganisms through several parallel non-specific mechanisms, which include damage to the microorganism's envelope, both to its lipid and protein content, and to intracellular proteins and nucleic acids (for a recent review see [13]). Many bacteria and fungi have different mechanisms to deal with excess copper (reviewed in [12]). However, above a certain threshold and time of exposure, they cannot deal with the copper overload and die. In contrast to the highly resistant microbes that have evolved to antibiotics in less than 50 years of use, tolerant microorganisms to copper are extremely rare even though copper has been a part of the earth for millions of years. This can be explained by the multisite and non-specific kill mechanisms of copper [12]. Significantly, copper displays potent biocidal activity also against antibiotic resistant bacteria and antiviral resistant viruses [14-16].

Today, different copper containing compounds are being used as algaecides, fungicides, bactericides, molluscicides, wood preservatives, and in paints as antifouling agents [17,18]. Furthermore, copper and copper-based compounds are routinely used in several health-related areas. These include 1) control of *Legionella* [19-23] and other bacteria [24] in hospital water distribution systems; 2) prevention of algae and other parasites growth in potable water reservoirs (e.g. [25,26]); 3) reduction of caries in dentistry [27,28]; 4) reduction of foodborne diseases [14,15,29-35]; 5) reduction of transmission of health-associated (nosocomial) pathogens in hospitals, clinics, and elderly homes [36-39]; and 6) birth control [40,41]. The U.S. Environmental Protection Agency (EPA) in March 2008 approved the registration of copper alloys as materials with antimicrobial properties, making copper as the only metal that can be used in hospitals in order to reduce bioburden and for which public health claims can be made.

## NOVEL COPPER HEALTH RELATED APPLICATIONS

Recently, a novel durable platform technology has been developed, which embeds copper oxide particles into polymeric materials [14,15]. Copper oxide is considered a non-soluble form of copper, as it does not solubilize in an aqueous solution of a pH 5.5 and above. As such, copper oxide particles serve as a reservoir of copper ions that are slowly liberated in the presence of humidity, such as that present in the interior of the shoe or in the skin surface. Thus, the introduction of copper oxide particles into polymeric materials endows them with potent broad-spectrum anti-microbial (anti-bacterial, anti-viral, anti-fungal) [14-16], anti-mite properties [14,42], and in some applications has a direct effect on physiological processes, such as enhanced wound healing [9].

The innovative current or potential uses of this technology in health-related applications include a) making hospital sheets, patient robes, patient pajamas, and nurse clothing, from copper-oxide impregnated biocidal textiles, with the aim of reducing bioburden and nosocomial infections [14,15,43,44]; b) producing acaricidal mattresses, quilts, carpets, and pillows that may improve the quality of life of those suffering from dust-mite related allergies [14,42]; c) using copper-impregnated socks for the prevention and treatment of fungal foot infections (athlete's foot) [45]; d) using copper-impregnated socks for reducing the risk of skin pathologies, especially in diabetic patients with compromised blood supply to the extremities [10]; e) producing antiviral and antibacterial copper-impregnated personal protective equipment (PPE), such as protective respiratory masks [44]; f) using pillowcases that improve the facial skin characteristics, such as reduction of wrinkles [46]; and g) using copper oxide containing wound dressings for the reduction of dressing and wound contamination and enhancement of wound repair [9,47].

The copper oxide load in the above described products is typically 1% weight of the copper oxide particles per weight of the polymeric material in which the copper oxide particles are impregnated. In some applications, such as in the wound dressings [9,47] and antiviral respiratory mask [44], the concentration of the copper oxide in the products is 3% (w/w). Most of the copper oxide particles are embedded within the polymeric product, however only some of the particles and part of these particles actually are exposed to the surface of the product (Fig. **1**) and are in possible contact with the user.

## BRIEF OVERVIEW OF THE SAFETY OF COPPER

Throughout history copper has been used by man in many daily day products, such as in utensils and adornments. Furthermore, copper has been used for medicinal purposes by different civilizations, e.g. by the ancient Egyptians, Greeks, Romans, and Aztecs, who topically or systemically treated various diseases with different forms of copper and copper compounds (such as copper carbonate, copper silicate, copper oxide, copper sulfate, and copper chloride) [11]. Today, a much known example of the use of copper in medicine is its use for the prevention of conception. Copper intrauterine devices are being widely used by millions of women, are approved by the regulatory agencies (e.g. USA FDA) and has been in practice for several decades and are considered very safe [41,48,49]. However, copper is not appropriate for use for systemic infections, because once copper is ingested, it readily interacts with transport proteins as well as small molecular weight ligands [5,7], making it unavailable as an antimicrobial. Also, people with Wilson's disease, a rare metabolic genetic hepatic disorder, cannot metabolize copper, which accumulates in the tissues.

Following a recent thorough and extensive analysis of all available information on the toxicity, use practices, and exposure scenarios, and the environmental behavior of copper, conducted by a panel of experts, the USA EPA has allowed the use of copper and copper compounds in many applica-

tions, such as pesticide on crops, herbicide, wood preservation, and for direct aquatic applications. As stated by the agency - "Copper is a naturally occurring metal that is efficiently regulated in the human system and current available literature and studies do not indicate any systemic toxicity associated with copper exposure" [50].

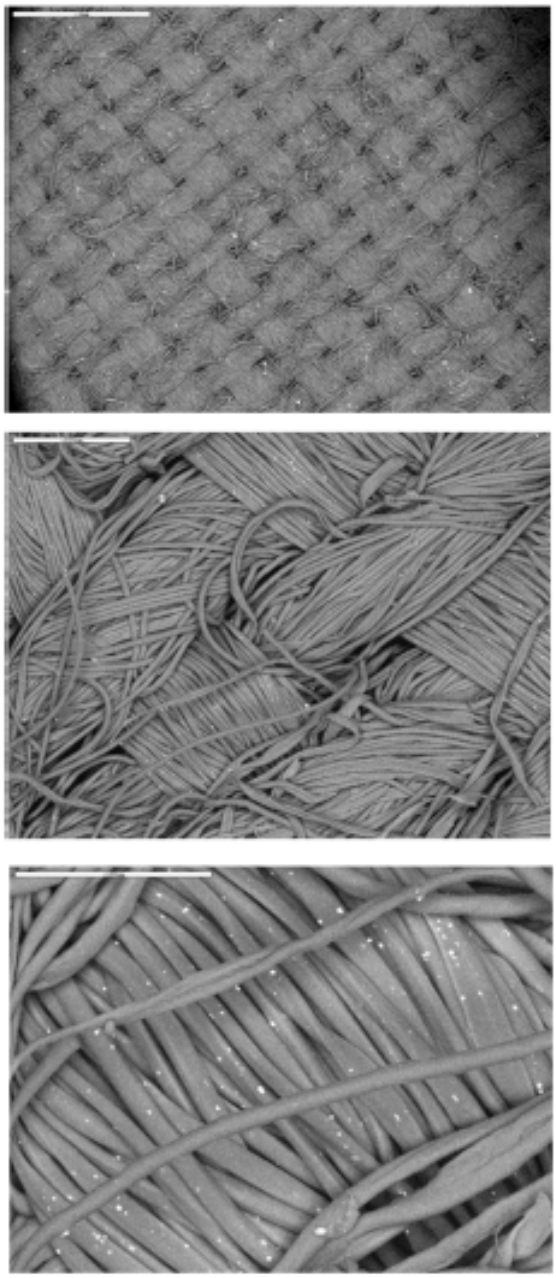

**Fig. (1).** Scanning electronic microscope pictures of a fabric impregnated with copper oxide particles. Yarn in weft contains the copper oxide particles (white dots).

Since copper oxide is an inorganic insoluble compound, most toxicity studies have been performed with soluble copper forms. Thus, not many studies have addressed copper oxide toxicity per se. In the few studies in which copper oxide has been studied directly, its safety was found to be similar to that reported to other copper compounds. For example, oral toxicity studies were done in animals. In cattle receiving a single 40 gram oral dose of copper oxide particles, no biochemical evidence of toxicity was recorded [51]. Sheep receiving 10 grams of copper oxide particles for 65 consecutive days did not show any signs of clinical toxicity [52,53]. Indeed, copper oxide is used as a source of copper in mineral and vitamin supplements for animals and humans too and is considered safe (e.g. http://www.empr.com/vitaminsmineralssupplements/centrum/drug/5901/).

While the safety of copper compounds and specifically copper oxide can be more extensively reviewed, the focus of the current manuscript is to review the safety of the use of copper oxide in consumer and medical device products that come in contact with the skin (following chapter).

## DERMAL EXPOSURE TO COPPER OXIDE IMPREGNATED PRODUCTS – SAFETY STUDIES

The following chapter will review the safety non-clinical and clinical studies conducted with products containing copper oxide that come in contact with open and closed skin (Table 1).

### Non Clinical Studies

#### *Guinea-Pig Maximization Test*

This test was conducted according to the ISO 10993-10 (1994) guidelines for determining allergenicity of new chemicals. The test consisted of an induction phase during which 10 test guinea pigs (Hartley) were sensitized by intradermal injections of test fabrics extracts containing 0.4% copper oxide weight/weight (w/w) and 14 days later (to allow for a potential reaction of the immune system) the animals were challenged with the extracts of the test fabrics on their skin. The degree of skin reactions was compared to five guinea pigs (control animals), which were treated with only the extraction medium (saline) during the induction phase and with the extract of the test fabrics during the challenge phase. None of the ten animals exposed to extracts of test fabrics showed allergic skin reactions as compared to the control animals exposed to the extraction vehicle only. Similar normal food intake and weight gain were presented by animals of both groups throughout the test period [14].

#### *Rabbit Skin Irritation Tests*

The potential dermal irritation and delayed-type hypersensitivity of products containing 0.4%, 0.5%, 1%, 2.3%, and 3% copper oxide (w/w), were assessed in New Zealand Whites (NZW) female rabbits according to the International Standard ISO 10993-10:2002 (E)Second Edition 01 September 2002, Biological Evaluation of Medical Devices-Part 10: Tests for Irritation and Delayed-Type Hypersensitivity. Section 6.3. Animal Skin Irritation Test. Briefly, different sites in each test animal in which the fur was removed were exposed to either a test product or to a similar product not containing copper oxide. Following application, each test site or control site was prepared for a total duration of 4 hours. At the end of the contact time, the products were removed and dermal reactions for erythema, eschar, and edema formation were scored according to the test guidelines and recorded at the standard time points of 1, 24, 48, and 72 hours after

product removal. No dermal reactions or any other adverse clinical signs were noted throughout the entire observation periods. The calculated guideline-based Primary Irritation Index (PII) was 0.0 for all test items, i.e., the products containing even 3% copper oxide w/w were classified as a non-skin irritant item under ISO-10993 international standard. In addition, no systemic clinical signs in reaction to treatment were evident in any of the animals and no unusual changes in body weight were noted [14,15,44,47].

### *Porcine Partial Thickness Wound Test*

The skin of pigs is considered the closest model to human skin in terms of the anatomical and physiological characteristics [54]. The possible adverse effects of applying a wound dressing containing 2.3% copper oxide (w/w) on wounds were examined using a porcine partial thickness wound model. Test sites comprised a total of 12 evenly bilateral allocated punch biopsy partial thickness wounds, each measuring about 12 mm in diameter and 5 mm in depth. Immediately following wounding, six randomly chosen wounds were covered with test dressings and the remaining six wounds with control commercial sterile dressing pads. Macroscopic examination of the wound sites revealed no significant differences between the control and test dressings in erythema, edema, and crust formation at 3 and 7 days post-wounding. Microscopic examination and histological analyses of the test site biopsies harvested 3 days post-wounding revealed no difference between the control and test dressings treatments at all test sites. Seven days post-wounding, the examined biopsies of dermal test sites exposed to both control and copper oxide containing wound dressings demonstrated a "wet" phlegmoneus eosinophilic dermatitis and granulomatous foreign body cell reaction to the same extent. All clinical pathology values obtained from the pre- and 2 post-treatment collected blood samples were similar and within the normal range [47].

### *Diabetic Mice Wound Model*

In several experiments using diabetic mice (db/db) the mechanisms of enhanced wound healing endowed to wound dressings by impregnating them with 2.3% copper oxide w/w were studied [9]. In these experiments the safety of wound dressings was examined too. Briefly, a circular 6-mm full-thickness single skin wound was surgically created on the dorsum of each animal (n=30) and the entire wound test site was then directly and continuously covered by a 20x20 mm dressing containing copper oxide. As control, similar wound dressing, but without any impregnated copper oxide, was used (n=30). Three animals per group were euthanized and the entire semi-occlusive dressing was carefully removed from the animals at different time points (days) following the animals wounding. Histopathological analysis of skin specimens taken from the wounds of diabetic mice that were treated with control dressings or copper dressings showed a similar normal wound healing process in both treated groups, including epidermal regeneration and granulation tissue formation, with numerous new blood vessels, chronic inflammatory infiltrate, generation of new hair follicles and sebaceous glands, and fibroplasia. There were no signs of adverse reactions, precancerous changes or atypia of any kind in both groups of mice, indicating that the presence of 2.3% copper oxide w/w in the wound dressings had no adverse effects on the healing skin, even when present on the wound for 3 weeks.

### *Elution Safety Studies*

The impregnation of copper oxide (~3% w/w) into respiratory protective face masks endows them with potent anti-influenza biocidal properties without altering their physical barrier properties [44]. The use of biocidal masks may significantly reduce the risk of hand or environmental contamination, and thereby subsequent infection, due to improper handling and disposal of the masks. Several tests conducted under GLP in independent labs determined that the amount of copper eluted in the air from the copper oxide impregnated mask during 5 hours under simulated breathing conditions was 0.467 ± 0.47 pg, a level that is far below ($>10^5$ folds) the respiratory copper permissible exposure limit (PEL) set by the USA Occupational Safety and Health Administration ("OSHA"). The lowest observed-adverse-effect levels ("LOAELs") for chronic copper inhalation exposure were determined to be 0.64 mg/m$^3$ [55]. Again, the copper levels eluted during the simulated breathing test from the copper containing masks (0.09 pg/m$^3$) are a tiny fraction ($>10^6$ folds) of this copper LOAEL. Furthermore, even when simulating a worst case scenario, in which the masks would be soaked in saliva, and all the saliva would be ingested, the amount of copper eluted from the mask into the saliva was ~7.24 µg/hr, which is significantly lower than 20.8 µg/hr, the minimal risk level (MRL) for oral exposure for a person weighing 50 kg [56].

## Clinical Studies

Several clinical studies have been performed to test both the efficacy and safety of different textile products containing copper oxide (Table 1). The following summarizes the safety results obtained from these studies as related to the contact of the products with different areas of the body.

### *Facial Skin*

The safety of copper oxide containing products on the facial skin was tested in 5 double blind, randomized, placebo controlled clinical studies. Four studies were performed with pillowcases containing 0.8% and 1% copper oxide w/w (2 studies for each concentration) and one study was conducted with a face mask containing 0.8% copper oxide w/w. The studies were performed by independent researchers and specialized labs in order to demonstrate the safety and efficacy of these products in reducing wrinkles and improving the wellbeing of the skin. A total of 150 individuals used the test products containing copper oxide while 150 individuals used placebo control products. In 4 studies, the products were used daily for 28 days. In one trial the pillowcases were used daily for 56 days. In all 5 studies, no skin irritation (irritation scores = 0) or any other adverse reactions of effects were registered, as determined by expert graders (dermatologists or trained technicians) who examined the study participants every two weeks during the studies. On the contrary, all studies demonstrated improvement in several facial skin related attributes (e.g. [46]).

**Table 1. Safety Studies Conducted with Products Containing Copper oxide.**

| | Study/Test | Copper Oxide Load (% w/w) | Outcome | Reference |
|---|---|---|---|---|
| **Non Clinical** | Guinea-Pig Maximization Test | 0.4 | No allergenicity | [14] |
| | Rabbit Skin Irritation Tests | 0.4-3% | No irritation | [14,15,44,47] |
| | Porcine Partial Thickness Wound Test | 2.3 | Normal erythema, edema, and crust formation. Normal clinical pathology and wound healing | [47] |
| | Diabetic Mice Wound Model | 2.3 | No adverse reactions, precancerous changes or atypia. Enhanced wound healing | [9] |
| | Elution safety studies | 3 | Copper levels eluting through air or saliva safe - below LOAEL and MRL | [44] |
| **Clinical Trials** | Facial skin | 0.8-1 | No skin irritation or adverse effects | [46] and in press |
| | Hands skin | 1 | No skin irritation or adverse effects | Unpublished data |
| | Thigh skin | 1 | No skin irritation or adverse effects | Unpublished data |
| | Foot skin | 0.5 | No skin irritation or adverse effects | [45, 57] |
| | Whole body | 0.2 | No adverse effects | [15] |

### *Hands Skin*

The safety of copper oxide containing products on the hand skin was tested in a double blind, randomized, placebo controlled clinical study. Sixty four women participated in the study. Thirty two women wore control gloves and 32 women wore similar gloves containing 1% copper oxide w/w while sleeping for a period of one month. The women were examined by a dermatologist at the beginning of the study and after 2 and 4 weeks of wearing the gloves. No skin irritation, skin sensitization or any other adverse reaction was noted.

### *Thigh Skin*

The safety of copper oxide containing tights when in contact with the thigh area was determined in a double blind study with 30 female subjects that were supplied with tights with the copper oxide impregnation (1% copper oxide w/w load) restricted to either the left or right leg. The allocation of copper oxide to the left or right leg was unknown to the investigator or to the study participants. Subjects were instructed to wear the tights daily for at least 12 hours per day over a four week period. The right and left thighs were assessed by a dermatologist and by using objective methods (Corneometer, D-Squame adhesive discs), at 0, 2, and 4 weeks of using the tights. No skin irritancy or any adverse events were recorded in any participant.

### *Foot Skin*

The safety of copper oxide containing products on the foot skin was determined in several studies. A feasibility study evaluated the safety and efficacy of copper oxide containing socks (0.5% copper oxide w/w) in 56 subjects with tinea pedis. A variety of podiatric conditions were examined (erythema, itching, burning, scaling, vesicular eruptions, fissuring, drainage, odor, and edema). The copper containing socks were shown to be safe and effective in treating tinea pedis [45]. Treated subjects had significant improvement or complete response in all podiatric condition examined. Importantly, not even one adverse event was reported. Furthermore, in no instance did a patient who had no specific problem develop one. Of note, ~ 40% of the patients studied were diabetic, in whom the capacity to deal with skin damage, for example, is significantly reduced, but still no negative effects were noted, on the contrary [45].

Another study was conducted in a trial with 53 soldiers undergoing basic training. The soldiers received socks containing 0.5% copper oxide w/w in the sole of the socks. The soldiers used the socks daily for 3 weeks. Significant positive results in one or several of the attributes examined regarding athlete's foot infections were recorded, without occurrence of any adverse events [57]. Similarly, no adverse reactions were recorded in a second trial with socks containing 0.7% copper oxide w/w in which ~ 200 soldiers used the socks continuously for one week under harsh field conditions. The test showed excellent results in protecting the feet of the soldiers and reducing significantly the number of soldiers reporting to the infirmary due to foot problems [57]. Based on this test this army has recently started to equip all their soldiers with copper oxide containing socks. It should be pointed out that socks containing up to 1% copper oxide w/w are sold worldwide in the consumer market for more than 5 years without any known reports of adverse effects.

Another feasibility study, conducted at the Department of Internal Medicine in Barzilai Medical Center in Israel, evaluated safety and toxicology profile of copper oxide containing sheets (0.2% w/w load). A group of patients slept on

the Cupron sheets for a total of 300 nights. No adverse events were reported [15].

## IN CONCLUSION

Copper is an essential trace element for humans. Its use in medical devices is considered safe to humans, as demonstrated by the widespread (millions of women) and prolonged (more than 10 years by a single individual) use by women of copper intrauterine devices [41,48,49]. The use of copper oxide in consumer and medical products that come in contact with skin is safe. The lack of adverse reactions due to exposure of skin to copper oxide impregnated products, as described above, is in accordance with the extremely low risk of adverse reactions due to dermal contact with copper [58,59], including in wounds [8], and with copper being an integral component of many of the over-the-counter treatments for wound healing [60,61].

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## CONFLICT OF INTEREST

Dr. Borkow is the Chief Medical Scientist of Cupron Inc., the company that has developed and owns the technology of incorporating copper oxide particles into polymeric materials.

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