

# Technical Guidance for the Classification of Copper Metal Under the Globally Harmonized System for Classification and Labelling of Chemicals (GHS)

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# Executive Summary

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The purpose of this document is to serve as a technical resource describing the hazard classification of copper metal according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), 7<sup>th</sup> Revised Edition (UN, 2017). This document outlines physical hazard classifications that are applicable to all three forms of copper metal evaluated herein and presents the classifications for human health and environmental hazards for all three forms. This document is intended to help guide regulators and industry groups by providing endpoint-specific hazard classifications that are based on the best available science, along with justifications that outline the classification decision-making process.

The three forms of copper metal covered in the document are copper massive, copper powder, and copper flakes coated with aliphatic acid (hereafter, "coated copper flakes"). Copper massive and copper powder fall under Chemical Abstracts Service Registration Number (CAS#) 7440-50-8, while coated copper flakes has no CAS # assigned, according to the European Union's Harmonized Classification, Labelling, and Packaging (CLP) regulation. A form of copper metal called "granulated copper" has been identified as an active substance under the European Union Biocidal Products Regulation, but this form is not discussed separately here, because granulated copper would not normally be identified as a separate form of copper under GHS (see, for example, GHS Section A9.7.5.4; UN, 2017).

This document does not assess hazards for other inorganic copper compounds (*e.g.*, copper sulfate or copper oxides) or nanoform copper. The recommended hazard classifications presented within this document are not specific to any one jurisdiction, but rather reflect globally compliant classifications according to the 7<sup>th</sup> Revised Edition of the GHS guidelines (UN, 2017).

For each hazard endpoint, a weight-of-evidence (WoE) evaluation of the data (*i.e.*, considering all available information characterizing a property or toxicological endpoint, including the quality and consistency of *in silico*, *in vitro*, *in vivo*, and human data) was conducted that considered data for the most relevant forms of copper. When data were not available for a particular endpoint, a read-across approach was applied in which experimental data were extrapolated from other copper forms and compounds. It is important to note that coated copper flakes are chemically and toxicologically different from other copper compounds, and thus this form was evaluated by primarily using data specifically for coated copper flakes.

Based on all the available information, the resulting GHS human health and environmental hazard classifications for the three forms of copper metal evaluated in this document are summarized in Table ES.1. If a classification for a specific chemical, physical, or toxicological endpoint is not listed below, then the WoE suggests that no hazard classification is necessary.

**Table ES.1 Summary of GHS Hazard Classifications for Copper Metal**

<b>Copper Metal Form</b>	<b>GHS Hazard Classifications</b>
Copper Massive CAS: 7440-50-8, EC: 231-159-6	Acute Aquatic Toxicity Category 3
Copper Powder CAS: 7440-50-8, EC: 231-159-6	Acute Aquatic Toxicity Category 1 (M factor = 1) Chronic Aquatic Toxicity Category 3
Coated Copper Flakes No CAS or EC numbers allocated	Acute Oral Toxicity Category 4 Acute Inhalation Toxicity Category 3 Eye Irritation Category 2A Acute Aquatic Toxicity Category 1 (M factor = 10) Chronic Aquatic Toxicity Category 2

Notes:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017); M Factor = Multiplying Factor.

# 1 Introduction and Scope

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In 2003, the United Nations published the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), establishing a standardized framework for classifying chemical hazards and communicating hazard information through safety data sheets and labels. The GHS guidance document has subsequently been revised, for example, in 2017 as the 7<sup>th</sup> Revised Edition (UN, 2017). The objective of this guidance is to present a harmonized framework for communicating the physical, chemical, and toxicological hazards of chemicals for human health and the environment to allow for safety precautions to be implemented during the use or transport of chemical substances or mixtures. The GHS framework is comprised of "building blocks," which are combinations of measurable endpoints (*e.g.*, boiling point or acute toxicity) and hazard categories (including "not classified") to which a chemical may be assigned. Hazard categories vary by endpoint and are often designated numerically, with Category 1 representing the greatest hazard. For many hazard endpoints, there is a high-end dose limit, such that effects observed above this dose are not classifiable.

Although the objective of the GHS is to create a globally harmonized system, implementing countries are free to determine which building blocks to adopt and to make adaptations to the classification criteria. As a consequence, there are jurisdictions that have not implemented the GHS or that have only partially adopted the GHS hazard categories. Another factor that may result in discordant hazard classifications is that jurisdictions have adopted different editions of the GHS guidance as the basis of their regulations and classification systems. In addition, although the GHS outlines the process and specifies the criteria for assigning hazards, expert judgment must also be applied. These factors have resulted in discordant hazard classifications for copper metal forms across jurisdictions, although this issue is certainly not unique to copper.

Copper is a naturally occurring element that is commonly found in the environment. Copper metal is widely used in industrial and commercial applications, because it has a number of key physical properties, including conductivity, malleability, and corrosion resistance (ECI, 2008). This document summarizes physico-chemical, toxicological, ecotoxicological information, and associated hazard classifications for copper massive/copper powder (which fall under CAS# 7440-50-8) and copper flakes coated with aliphatic acid (hereafter, "coated copper flakes"; no CAS#) for endpoints covered under the GHS. This document focuses on synthesizing and interpreting data, assigning GHS hazard classifications to the aforementioned forms of copper metal, and providing explicit justification for those hazard classifications. The defining properties and bioaccessibility of the copper metal forms assessed in this document are summarized in Table 1.1.

**Table 1.1 Defining Properties and Bioaccessibility of Copper Metal Forms**

Form of Copper Metal	Particle Size	Composition	Specific Surface Area	Bioaccessibility <sup>1</sup>
Copper Massive CAS: 7440-50-8 EC: 231-159-6	>1 mm	>99.9% Cu	≤0.67 mm <sup>2</sup> /mg	0.10%
Copper Powder CAS: 7440-50-8 EC: 231-159-6	<1 mm	99.7% Cu, 0.3% Cu <sub>2</sub> O	≥0.67 mm <sup>2</sup> /mg	1.1-7.3%
Coated Copper Flakes No CAS or EC numbers allocated	0.008-0.011 mm	93.7-96.3% Cu, 1-2.6% Cu <sub>2</sub> O, 2.8-3.9% organic content <sup>2</sup>	2,900 mm <sup>2</sup> /mg (average)	41.6-71.5%

Notes:

ASTM = American Society for Testing and Materials; Cu = Copper; Cu<sub>2</sub>O = Cuprous Oxide; NA = Not Applicable.

Source: Chemical Safety Report for Copper (ECI, 2018a).

(1) Bioaccessibility was determined by the release of copper ions in artificial gastric fluid (in accordance with ASTM D5517-07) (Rodriguez *et al.*, 2010, as cited in ECI, 2018a).

(2) Organic content as measured by loss on ignition (ECI, 2018a).

Copper massive and powder are defined by their particle size and specific surface area (SSA; see Table 1.1). In line with the GHS guidance, Section A9.7.5.4, a particle size cut-off of 1 mm distinguishes the two forms (UN, 2017). However, because it has been established that the environmental hazards of copper depend on the exposed surface area, this cut-off could also be expressed as SSA (ECI, 2018b). A copper sphere (with a density of 8,960 kg/m<sup>3</sup>) of 1 mm diameter has an SSA of 0.67 mm<sup>2</sup>/mg, and this value can be used as an alternative, surface area-based cut-off between copper powder and copper massive.

"Granulated copper" has been identified as an active substance under the European Union Biocidal Products Regulation, but this form is not discussed separately here, because granulated copper would normally not be identified as distinct from copper massive under GHS (see, for example, GHS Section A9.7.5.4; UN, 2017).

In contrast, coated copper flakes are comprised of copper metal flakes produced through a very specific process (*e.g.*, ball-milling) and surrounded by aliphatic acids (*e.g.*, stearic acid and zinc stearate) that prevent aggregation. Due to this, coated copper flakes have a very high reactive surface area compared to the other two forms of copper metal assessed herein. This document does not assess the hazards of other inorganic copper compounds, such as copper oxides and copper sulfates, although toxicological data from these forms are used for read-across in the weight-of-evidence (WoE) evaluations of copper massive, copper powder, and coated copper flakes, when applicable. In addition, this assessment excludes nanoforms of copper.

Due to the number of chemical, physical, and toxicological endpoints considered under the GHS, multiple types of data (of varying complexity) need to be assessed to determine a hazard classification for a compound. Often, multiple datasets are available for a compound for a certain endpoint, and these datasets may be conflicting, inadequate, or inconsistent. The GHS guidance identifies tools such as WoE, read-across, and expert judgment that can be applied when complex data interpretation is necessary (UN, 2017). WoE evaluation is the process of evaluating one or more lines of evidence and integrating the results, considering the strengths and weaknesses of the evidence, to reach a justifiable conclusion. Read-across is when the toxicological properties of a well-studied (data-rich) chemical, called a surrogate or analog, are "read across" to a less-studied (data-poor) chemical. Using a read-across approach, experimental data were extrapolated from copper forms and compounds to reach hazard conclusions for the



forms of copper metal assessed in this report, when necessary. Expert judgment was often also required for interpreting the various datasets available for the assessed copper compounds, based on prior experience with certain test methods, chemical classes, or quantitative analysis procedures.

The GHS framework includes 17 physical endpoints, 12 human health endpoints, and 3 environmental endpoints (Table 1.2). A number of the physical hazards are specific to particular physical forms (*i.e.*, liquid or gas) and, as such, are not applicable to copper metal. The applicable physical hazards for copper metal are presented in Section 2 of this document. Although not a required GHS hazard endpoint, "combustible dust" is included in Annex 4 of the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017). The 7<sup>th</sup> Revised Edition of the GHS guidance presents combustible dust as an important endpoint to assess, because combustible dust is a mandatory category that needs to be filled out for safety data sheets in the United States. The human health and environmental hazard classifications for each of the three forms of copper metal evaluated herein are presented in Sections 3 and 4, respectively. The two primary environmental hazards, acute and chronic aquatic toxicity, have been well-studied in relation to copper metal (and, more specifically, copper ions). The approach to hazard classification of relatively insoluble metals such as copper is different from that for organic compounds, with a number of specific guiding principles and study designs. This document outlines the overall approach taken for aquatic toxicity hazard classification for copper massive, copper powder, and coated copper flakes, but an in-depth review of all aspects of the environmental hazard classification process is outside the scope of this document. As such, this document will focus on integrating and interpreting the results of only the most recent studies of the possible environmental hazards posed by copper in the context of GHS classification.

The recommended hazard classifications discussed within this document are based on a WoE evaluation of the currently available data for the three forms of copper metal that were evaluated. The subsequent report sections outline the endpoint-specific data for each form of copper metal, using data for other forms when necessary, and presents an interpretation of the data to support the final recommended hazard classification for each GHS hazard endpoint. This document is intended to serve as a reference for regulators during the process of determining GHS hazard classifications for copper metal. It is important to note, however, that the hazard classifications presented in this document do not override any jurisdiction-specific harmonized or other legally binding hazard classifications (*e.g.*, European Union's Harmonized Classification, Labelling, and Packaging [CLP] classifications for coated copper flakes). This document is intended to be consistent with the 7<sup>th</sup> Revised Edition of the GHS guidance and will be updated as appropriate as new data become available. The recommended hazard classifications discussed herein are compliant with the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017).

**Table 1.2 Globally Harmonized System of Classification and Labelling of Chemicals Hazard Endpoints and Categories**

<b>Hazard Endpoints</b>	<b>Possible Hazard Categories</b>
<b>Physical Hazards</b>	
Explosives	Unstable explosive, Division 1.1-1.6
Flammable Gases	Flammable gas (1A, 1B, 2), Pyrophoric gas, Chemically unstable gas (A, B)
Aerosols	Category 1, 2, 3
Oxidizing Gases	Category 1
Gases Under Pressure	Compressed gas, Liquefied gas, Refrigerated liquefied gas, Dissolved gas
Flammable Liquids	Category 1, 2, 3, 4
Flammable Solids	Category 1,2
Self-reactive Substances and Mixtures	Type A-G
Pyrophoric Liquids	Category 1
Pyrophoric Solids	Category 1
Self-heating Substances and Mixtures	Category 1,2
Substances and Mixtures That, in Contact with Water, Emit Flammable Gases	Category 1, 2, 3
Oxidizing Liquids	Category 1, 2, 3
Oxidizing Solids	Category 1, 2, 3
Organic Peroxides	Type A-G
Corrosive to Metals	Category 1
Desensitized Explosives	Category 1, 2, 3, 4
<b>Human Health Hazards</b>	
Acute Toxicity – Oral	Category 1, 2, 3, 4, 5
Acute Toxicity – Dermal	Category 1, 2, 3, 4, 5
Acute Toxicity – Inhalation	Category 1, 2, 3, 4, 5
Skin Corrosion/Irritation	Category 1, 2, 3
Serious Eye Damage/Eye Irritation	Category 1, 2, 2A, 2B
Respiratory or Skin Sensitization	Respiratory Category 1, 1A, 1B; Skin Category 1, 1A, 1B
Germ Cell Mutagenicity	Category 1, 1A, 1B, 2
Carcinogenicity	Category 1, 1A, 1B, 2
Reproductive Toxicity	Category 1, 1A, 1B, 2; Category for effects on or <i>via</i> lactation
Specific Target Organ Toxicity – Single Exposure	Category 1, 2, 3
Specific Target Organ Toxicity – Repeated Exposure	Category 1, 2
Aspiration Hazard	Category 1, 2
<b>Environmental Hazards</b>	
Hazardous to the Aquatic Environment – Acute	Category 1, 2, 3
Hazardous to the Aquatic Environment – Chronic	Category 1, 2, 3, 4
Hazardous to the Ozone Layer	Category 1

Note:

Source: UN (2017).

## 2 Physical Hazard Classifications

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Copper metal is not classified for any physical hazards under the GHS. The basic physical and chemical properties of the different forms of copper metal assessed herein are presented in Table 2.1. The three forms of copper metal evaluated in this document are defined primarily by particle size and surface area. At a constant volume, surface area and particle size are inversely proportional, such that surface area increases as particle size decreases. Copper massive takes the form of various shapes (*e.g.*, wire, rod, and sheet) and is defined by a particle size greater than 1 mm and an SSA less than or equal to 0.67 mm<sup>2</sup>/mg (ECI, 2018a). Copper powder is generally defined by a particle size less than 1 mm and an SSA greater than 0.67 mm<sup>2</sup>/mg. For the purposes of GHS hazard classification for this copper metal form, tests have been conducted with a representative fine copper powder with median particle size of 10 μm. Coated copper flakes' average particle size is 0.008-0.011 mm, with a measured SSA of 2,900 mm<sup>2</sup>/mg. The flakes are coated with an aliphatic acid (*e.g.*, steric acid), which prevents aggregation of the particles and greatly increases surface area (ANSES, 2013).

The physical hazard classifications presented in Section 2.1 are applicable to all three of the forms of copper metal evaluated in this document. Although not an official GHS endpoint, Section 2.2 discusses the combustible dust hazard of the three copper metal forms, because an evaluation of this hazard is required in the preparation of a safety data sheet in the United States.

**Table 2.1 Information on Basic Physical and Chemical Properties of Copper Metal Forms**

Endpoint	Copper Massive and Copper Powder (CAS# 7440-50-8)	Coated Copper Flakes (No CAS#)
Appearance	Solid. Copper-reddish color. <sup>1</sup>	Extremely fine powder, reddish color <sup>2</sup>
Odor	Odorless <sup>1</sup>	Odorless <sup>2</sup>
Odor Threshold	Not applicable	Not applicable
pH	Not applicable	Not applicable
Melting Point	1,059-1,069°C <sup>1</sup>	1,057-1,058°C <sup>1</sup>
Initial Boiling Point and Boiling Range	Not applicable	Not applicable
Flash Point	Not applicable	Not applicable
Evaporation Rate	Not applicable	Not applicable
Flammability (solid, gas)	Non-flammable <sup>1</sup>	Not highly flammable <sup>2</sup>
Upper/Lower Flammability or Explosive Limits	Not applicable	Not applicable
Vapor Pressure	Not applicable	7.5E-9 Pa (20°C), 1.8E-8 Pa (25°C), 8.4E-7 Pa (50°C) <sup>1</sup>
Relative Density	8.78 g/cm <sup>3</sup> at 20°C <sup>1</sup>	Tap density: 0.47 g/mL at 20°C <sup>1</sup>
Water Solubility	Insoluble <sup>1</sup>	Insoluble <sup>1</sup>
	Stirring and oxidation for 14 days (pH 6.3-7.6) resulted in <1 mg/L	pH 7-9: <1 mg/L pH 4: 192 mg/L
Partition Coefficient: n-Octanol/Water	Not applicable	Not applicable
Auto-ignition Temperature	No auto-ignition <sup>1</sup>	No auto-ignition <sup>1</sup>
Viscosity	Not applicable	Not applicable
Explosive Properties	Non-explosive. The substance does not contain chemical groups associated with explosive properties. <sup>1</sup>	Non-explosive. The substance does not contain chemical groups associated with explosive properties. <sup>1</sup>
Oxidizing Substance	Non-oxidizing substance <sup>1</sup>	Non-oxidizing substance <sup>1</sup>

Notes:

CAS# = Chemical Abstracts Service Registry Number; CLH = Harmonized Classification and Labeling.

(1) Chemical Safety Report for Copper (ECI, 2018a).

(2) CLH Report for Copper Flakes (ANSES, 2013).

## 2.1 Summary of Physical Hazard Classifications

Copper massive, copper powder, and coated copper flakes are not classified for the following applicable GHS physical hazards: explosiveness; flammable solid; self-reactive substances and mixtures; pyrophoric solids; self-heating substances and mixtures; substances and mixtures that, when in contact with water, emit flammable gases; oxidizing solids; corrosive to metals; or desensitized explosives. See Table 2.2 for a summary of the endpoints and details on the hazard classification decisions. The remaining eight GHS physical hazard endpoints (flammable gases, aerosols, oxidizing gases, gases under pressure, flammable liquids, pyrophoric liquids, oxidizing liquids, organic peroxides) were judged to be not applicable to these forms of copper metal.

**Table 2.2 Summary of GHS Physical Hazard Classifications for Copper Metal and Justification**

Endpoint	GHS Classification	Justification
Explosiveness	Not Classified	Absence of explosive functional groups/properties.
Flammable solid	Not Classified	Study with coated copper flakes found no burning when in contact with flame for 20 minutes (ECHA, 2018a). Supported by data for copper powder (ECHA, 2018a).
Self-reactive substances and mixtures	Not Classified	Absence of self-reactive functional groups/properties.
Pyrophoric solids	Not Classified	Copper powder is used to extinguish some combustible metal fires ( <i>e.g.</i> , lithium).
Self-heating substances and mixtures	Not Classified	No data available. Experience with copper metal forms indicates a lack of self-heating properties.
Substances and mixtures that, when in contact with water, emit flammable gases	Not Classified	Copper is not a metalloid. Finely divided copper will not react with water at standard temperature and pressure.
Oxidizing solids	Not Classified	Copper contains no oxygen, chlorine, or fluorine.
Corrosive to metals	Not Classified	No data available. Experience with copper metal forms indicates that they are not corrosive to metals.
Desensitized explosives	Not Classified	Absence of explosive functional groups/properties.

Note:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

## 2.2 Combustible Dust Considerations for Copper Metal

Currently, the combustible dust hazard category is unique to the United States Occupational Safety and Health Administration (OSHA) hazard classification scheme. The 7<sup>th</sup> Revised Edition of the GHS guidance addresses this hazard endpoint, along with other hazards that do not result in an official GHS classification, in Annex 4 (UN, 2017). The overall assessment of the available literature does not support listing copper metal as a combustible dust hazard.

OSHA's "Hazard Classification Guidance for Manufacturers, Importers, and Employers" (OSHA, 2016) does not contain an official definition of the term "combustible dust." OSHA's Combustible Dust National Emphasis Program (NEP) and the National Fire Protection Association (NFPA) generally define combustible dust as a solid combustible material composed of distinct particles that presents a fire or deflagration hazard when suspended at a sufficient concentration in air or some other oxidizing medium (NFPA, 2015; OSHA, 2016). When contained in an enclosed area (*e.g.*, enclosed building or chamber), combustible dusts present an explosion hazard. The most severe hazard arises from a series of cascading explosions initiated by a small dust explosion igniting and causing subsequent, often larger, explosions. Different dusts of the same chemical material can have different ignitability and explosibility characteristics, depending on physical characteristics such as particle size, shape, and moisture content. These physical characteristics can change during manufacturing, use, or while the material is being processed.

While the OSHA hazard classification guidance (OSHA, 2016) does not require testing chemicals (only collecting and analyzing currently available data on chemicals), collecting test data is recommended for ensuring worker safety and accurately classifying chemical hazards. Consistent with OSHA recommendations, the most appropriate way to determine whether a material should be classified as a combustible dust hazard is to test the material and its powder/dust forms according to the recommended American Society for Testing and Materials (ASTM) guideline tests and in accordance with standardized testing schemes (*e.g.*, NFPA, 2015).

OSHA and several NFPA standards include test results for various materials. Neither copper nor copper dusts are included in OSHA's list of combustible dusts (OSHA, 2008) or in NFPA's "Standard for Combustible Metals" (NFPA 484; NFPA, 2015). Germany's Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) also maintains a database of combustible dusts (the GESTIS-Dust-EX database; IFA, 2016); the database does not categorize the majority of copper substances (including copper [II], copper powder, copper drilling dust, and oxidized copper), even those with particle sizes <63 µm, as combustible dusts. Therefore, unlike the alkali metals (*e.g.*, sodium, potassium) or other known combustible metal dusts (*e.g.*, aluminum) (OSHA, 2008; NFPA, 2015; University of Pittsburgh, 2016), copper is not known to be combustible.

### 2.2.1 Dust Particle Size

In the absence of test data or in cases in which the test results were inconclusive, OSHA states that combustible dust classification may be based on particle size, if information on particle size is available (OSHA, 2016). As reviewed in OSHA's hazard classification guidance, both OSHA and NFPA (in its "Standard for the Prevention of Fire and Dust Explosions from the Manufacturing, Processing, and Handling of Combustible Particulate Solids" [NFPA 654]) once defined combustible dust as a "finely divided solid material 420 microns or smaller in diameter (material passing a U.S. No. 40 Standard Sieve) that presents a fire or explosion hazard when dispersed and ignited in air" (OSHA, 2016).

However, the most recent revisions to agency guidance on combustible dusts (*e.g.*, NFPA 652) indicate that substances with particles <500 µm, as well as those composed of particles (including fibers, flakes, and agglomerations of smaller particles) that do not pass through a No. 40 sieve but have "a surface-area-to-volume ratio sufficient to pose a deflagration hazard" (OSHA, 2016), can be considered combustible dusts. OSHA (2016, p. 383) also states:

[i]f the material will burn and contains a sufficient concentration of particles 420 microns or smaller to create a fire or deflagration hazard, then it should be classified as a combustible dust. A classifier may, if desired, instead use the 500 micron particle size (U.S. Sieve No. 35) threshold contained in more recent NFPA standards. Care must be used with this approach where the particles are fibers or flakes, or where agglomerations of smaller particles may be held together by static charges or by other means that would prevent the dust from passing through respective sieves No. 40 and 35, but would still present a fire or deflagration hazard.

While some forms of copper (*e.g.*, copper powder and coated copper flakes) may meet the particle size definition of combustible dust, the experimental data on copper (*i.e.*, from the GESTIS-Dust-EX database; IFA, 2016) do not support listing these forms as combustible dust hazards.

### 3 GHS Human Health Hazard Classifications

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In the absence of toxicological data on copper massive and copper powder, the hazard assessments for these copper forms are based on read-across to the more data-rich soluble copper compounds (*e.g.*, copper sulfate), less soluble copper compounds (*e.g.*, copper oxide), and fine coated copper flakes (which are coated with substances – *e.g.*, aliphatic acids – to increase the SSA of the flakes). Copper ions are assumed to be the toxic moiety responsible for effects observed *in vivo*, an assumption that is supported by the available database on copper substances. This assumption forms the basis of the read-across approach. For the hazard profiles of copper massive and copper powder, information on solubility and bioaccessibility was evaluated in combination with toxicological data on coated copper flakes and other copper compounds in the read-across approach. When high-quality data were identified for multiple copper substances or forms (*e.g.*, copper oxide, copper sulfate, and coated copper flakes), consideration was given to chemical properties such as particle size, bioaccessibility, and solubility to enable the selection of the most relevant surrogate, and thus the key study(ies), to read across. To evaluate potential systemic toxicity from repeated oral exposure, toxicological data from the more soluble copper forms may be read across to less soluble forms, when no toxicological data are available, as a conservative measure. To evaluate potential acute oral toxicity, *in vivo* toxicity data on several copper-containing substances were used in combination with oral bioaccessibility data to predict the oral toxicity of those copper forms without *in vivo* data. Bioaccessibility data are used to support the read-across rationale and help determine appropriate GHS hazard classifications for the forms of copper metal assessed herein without performing additional animal studies.

Toxicological information for copper compounds was primarily obtained from comprehensive assessments and regulatory documents, such as the Chemical Safety Report for Copper (CSR) (ECI, 2018a), the Harmonized Classification and Labeling (CLH) Report for Granulated Copper (ANSES, 2017), the CLH Report for Copper Flakes (coated with aliphatic acid) (ANSES, 2013), and the European Union Voluntary Risk Assessment for Copper (ECI, 2008), and supplemented with information in the Organization for Economic Co-operation and Development (OECD) Screening Information Dataset (SIDS) "Initial Assessment Profile and Initial Assessment Report for Copper and Copper Compounds" (OECD, 2010, 2014); the ECHA Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) registration document for copper (ECHA, 2018a); and the available scientific literature. A WoE approach was applied for each hazard endpoint (which are summarized in Table 3.1) and form of copper metal, with preference given to high-quality data. A discussion of the supporting data for the assigned hazard classification is provided for each endpoint.

In addition, aspiration hazard is not addressed separately in this document, because it is not applicable to copper metal (aspiration hazard is only applicable to hydrocarbons, ketones, and alcohol). Therefore, none of the copper metal forms are classified as aspiration hazards.

**Table 3.1 GHS Human Health Hazard Endpoints**

Hazard Endpoint	Definition
Acute Toxicity (Oral, Dermal, Inhalation)	" <i>Acute toxicity</i> refers to serious adverse health effects (i.e., lethality) occurring after a single or short-term oral, dermal or inhalation exposure to a substance or mixture."
Skin Corrosion/ Irritation	" <i>Skin corrosion</i> refers to the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis occurring after exposure to a substance or mixture."
	" <i>Skin irritation</i> refers to the production of reversible damage to the skin occurring after exposure to a substance or mixture."
Serious Eye Damage/ Eye Irritation	" <i>Serious eye damage</i> refers to the production of tissue damage in the eye, or serious physical decay of vision, which is not fully reversible, occurring after exposure of the eye to a substance or mixture."
	" <i>Eye irritation</i> refers to the production of changes in the eye, which are fully reversible, occurring after the exposure of the eye to a substance or mixture."
Respiratory or Skin Sensitization	" <i>Respiratory sensitization</i> refers to hypersensitivity of the airways occurring after inhalation of a substance or a mixture."
	" <i>Skin sensitization</i> refers to an allergic response occurring after skin contact with a substance or a mixture."
Germ Cell Mutagenicity	" <i>Germ cell mutagenicity</i> refers to heritable gene mutations, including heritable structural and numerical chromosome aberrations in germ cells occurring after exposure to a substance or mixture."
Carcinogenicity	" <i>Carcinogenicity</i> refers to the induction of cancer or an increase in the incidence of cancer occurring after exposure to a substance or mixture. Substances and mixtures which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans."
Reproductive Toxicity	" <i>Reproductive toxicity</i> refers to adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring, occurring after exposure to a substance or mixture."
Specific Target Organ Toxicity – Single Exposure	" <i>Specific target organ toxicity – single exposure</i> refers to specific, non-lethal toxic effects on target organs occurring after a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in chapters 3.1 to 3.7 and 3.10 [i.e., chapters on other hazard endpoints] are included (see also para. 3.8.1.6)."
Specific Target Organ Toxicity – Repeated Exposure	" <i>Specific target organ toxicity-repeated exposure</i> refers to specific toxic effects on target organs occurring after repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included."
Aspiration Hazard	" <i>Aspiration</i> means the entry of a liquid or solid chemical directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system."
	" <i>Aspiration hazard</i> refers to severe acute effects such as chemical pneumonia, pulmonary injury or death occurring after aspiration of a substance or mixture."

Notes:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals.

Source: UN (2017 [emphasis in original]).



### 3.1 Copper Massive

Copper massive does not meet the criteria for classification as hazardous under the GHS for any human health hazards, as detailed for each endpoint below.

Oral absorption data for animals and humans indicate a dose-dependent range for copper ion absorption after ingestion. The essential nutritive value of copper ions drives homeostasis, with copper absorption ranging between 20% (after high copper intake – near-toxicity) to 80% (after low copper intake – near-deficiency) for soluble copper compounds (ECI, 2008). A dermal absorption value of 0.3% has been observed for soluble and insoluble copper substances in solution or suspension from *in vitro* percutaneous tests of solid copper on human skin (Roper, 2003; Cage, 2003, both as cited in ECI, 2008). Copper massive does not pose a significant health hazard through inhalation because these particles cannot be inhaled (ISO, 1995). Table 3.2 presents the GHS human health hazard classifications for copper massive and a summary of the justification for each classification.

**Table 3.2 Summary of GHS Human Health Hazard Classifications for Copper Massive and Justification**

Endpoint	GHS Classification	Justification
Acute Oral Toxicity	Not Classified	No acute oral toxicity data are available for copper massive. For copper massive and other copper compounds, the common functional moiety is the copper ion. The difference between the release of copper ions from copper massive compared to that of other copper compounds with reliable toxicological data was used to infer the toxicity of copper massive. LD <sub>50</sub> values for these other copper compounds range from 160-8,718 mg/kg-bw (ECI, 2018a). The cut-off oral LD <sub>50</sub> for GHS classification is 2,000 mg/kg-bw ( <i>i.e.</i> , substances with LD <sub>50</sub> values above 2,000 mg/kg-bw are generally not classified as acute oral toxicants under the GHS). Considering the low bioaccessibility of copper massive ( $\leq 0.1\%$ ) in artificial gastric fluids (Rodriguez <i>et al.</i> , 2010, as cited in ECI, 2018a) and the generally high LD <sub>50</sub> values derived from animal studies with more bioaccessible copper compounds (including some >2,000 mg/kg-bw; Lheritier, 1994; Sanders, 2001a, 2002a, all as cited in ECI, 2018a), copper massive is not classified as an acute oral toxicity hazard under the GHS.
Acute Dermal Toxicity	Not Classified	No acute dermal toxicity data are available for copper massive. Therefore, high-quality studies of copper oxide, copper sulfate, and coated copper flakes, which have a similar or higher solubility in water (and are therefore assumed to be more bioavailable) and greater bioaccessibility in artificial gastric fluid than copper massive, were used for the hazard assessment of copper massive. These studies show that these copper compounds induce low acute toxicity <i>via</i> the dermal exposure route ( <i>i.e.</i> , LD <sub>50</sub> values >2,000 mg/kg-bw), which is consistent with the low expected dermal penetration of copper ions, the toxic moiety of copper substances. The cut-off dermal LD <sub>50</sub> for GHS classification is 2,000 mg/kg-bw ( <i>i.e.</i> , substances with LD <sub>50</sub> values above 2,000 mg/kg-bw are generally not classified as acute dermal toxicants under the GHS). Therefore, copper massive is not classified as an acute dermal toxicant based on LD <sub>50</sub> values >2,000 mg/kg-bw in rats in studies of copper oxide (Sanders, 2002b, as cited in ECI, 2018a), copper sulfate (Lheritier, 1993, as cited in ECI, 2018a), and coated copper flakes (Sanders, 2001b, as cited in ECI, 2018a).

**Table 3.2 Summary of GHS Human Health Hazard Classifications for Copper Massive and Justification**

Endpoint	GHS Classification	Justification
Acute Inhalation Toxicity	Not Classified	No acute inhalation toxicity data are available for copper massive. The particle size of copper massive is significantly greater than 10 µm (ISO, 1995), and therefore, copper massive is not respirable and poses no acute inhalation toxicity hazard.
Skin Corrosion/Irritation	Not Classified	No skin irritation data are available for copper massive. Therefore, relatively recent, high-quality studies of copper oxide and coated copper flakes, which have low solubility in water, similar to copper massive, were used for the hazard assessment of copper massive. GHS hazard classification for skin irritation is warranted when mean Draize scores (for erythema or edema) meet or exceed 1.5 in at least two of three test animals (UN, 2017). Therefore, copper massive is not classified as a skin irritant under the GHS based on the negative results (Draize scores = 0) of reliable studies of copper oxide and coated copper flakes in rabbits (Sanders, 2002c, as cited in ECI, 2018a; Sanders, 2001a, as cited in ECHA, 2018a).
Serious Eye Damage/Eye Irritation	Not Classified	No eye irritation data are available for copper massive. Copper in massive form is not classified as an eye irritant, because there is limited or no potential for exposure of the eye to particles larger than 1 mm. Such particles would be readily removed from the eye mechanically. Therefore, copper massive poses no serious eye damage/eye irritation hazard.
Respiratory or Skin Sensitization	Not Classified	No respiratory sensitization data are available for copper massive or other copper compounds. Therefore, there is no basis for classifying copper massive as a respiratory sensitizer.  No skin sensitization data are available for copper massive. Therefore, the hazard assessment for this compound is supported by a reliable guideline study for copper oxide (Sanders, 2002b, as cited in ECI, 2018a), which has low solubility in water, similar to copper massive. Based on the results of this study, copper massive is not classified as a dermal skin sensitization hazard under the GHS. Supporting unpublished animal studies and some evidence in humans indicate that copper substances are generally not skin sensitizers (ANSES, 2013; ECI, 2008).
Germ Cell Mutagenicity	Not Classified	No mutagenicity or genotoxicity data are available for copper massive. Therefore, studies of copper sulfate were used for read-across to copper massive. Using a surrogate copper compound with higher solubility in water and artificial biological fluids ( <i>e.g.</i> , copper sulfate) for read-across to copper massive is conservative, because the availability of copper ions (considered to be the toxic moiety of copper substances) for uptake is expected to be higher for the surrogate than for copper massive. Copper massive is thus not classified as a germ cell mutagenicity hazard under the GHS based on negative results from guideline <i>in vitro</i> and <i>in vivo</i> genotoxicity studies of copper sulfate (Ward, 1994; Riley, 1994, both as cited in ECI, 2018a).

**Table 3.2 Summary of GHS Human Health Hazard Classifications for Copper Massive and Justification**

Endpoint	GHS Classification	Justification
Carcinogenicity	Not Classified	No carcinogenicity data are available for copper massive, but relevant chronic animal studies of other copper substances, primarily copper sulfate, are available. Therefore, studies of copper sulfate were used for read-across to copper massive. Using data from a surrogate copper compound with higher solubility in water and artificial biological fluids ( <i>e.g.</i> , copper sulfate) for read-across to copper massive is conservative, because the availability of copper ions (considered to be the toxic moiety of copper substances) for uptake is expected to be higher for the surrogate than for copper massive. Copper massive is thus not classified as a carcinogenicity hazard based on negative findings from rodent carcinogenicity studies of copper sulfate (Carlton and Price, 1973; Burki and Okita, 1969; Harrison <i>et al.</i> , 1954, all as cited in ANSES, 2017) and supported by evidence in humans that indicates copper is not carcinogenic (ANSES, 2017).
Reproductive Toxicity	Not Classified	No reproductive or developmental toxicity data are available for copper massive, but reliable reproductive/developmental animal studies are available for copper sulfate and copper chloride. Therefore, studies of copper sulfate and copper chloride were used for read-across to copper massive. Using data from surrogate copper compounds with higher solubility in water and artificial biological fluids ( <i>e.g.</i> , copper sulfate and copper chloride) for read-across to copper massive is conservative, because the availability of copper ions (considered to be the toxic moiety of copper substances) for uptake is expected to be higher for the surrogates than for copper massive. Copper massive is thus not classified as a reproductive toxicity hazard under the GHS based on a lack of reproductive and developmental toxicity in a study in rats administered copper sulfate (Mylchreest, 2005, as cited in ECI, 2018a) and supported by a reproductive/developmental screening test in rats administered copper chloride (Chung <i>et al.</i> , 2008, as cited in ECI, 2018a).
Specific Target Organ Toxicity – Single Exposure	Not Classified	Because no single-exposure or acute toxicity data are available for copper massive, high-quality animal studies that are available on other copper substances for this endpoint, including studies of copper oxide (Sanders, 2002a,b, both as cited in ECI, 2018a), copper sulfate (Lehritier, 1993, 1994, both as cited in ECHA, 2018a), and coated copper flakes (Sanders, 2001b, as cited in ECHA, 2018a) were used in the hazard assessment. The results of these studies are supported by relevant human data for copper sulfate (Araya <i>et al.</i> , 2001, 2003, both as cited in ECI, 2018a; ECHA, 2014a). The GHS guidance cut-off values (LOAEL/LOAEC) for STOT – SE hazard classification are 2,000 mg/kg-bw for oral and dermal exposures and 5 mg/L for inhalation exposure (for dust/mist/fume) (UN, 2017). Copper massive is thus not classified as a STOT – SE hazard under the GHS based on a lack of target organ effects in animals after acute oral and dermal exposures to the aforementioned surrogate copper compounds at levels requiring GHS classification. Regarding inhalation exposure, the particle size of copper massive is >1 mm, and therefore these particles are not respirable and pose no specific target organ toxicity hazard <i>via</i> the inhalation exposure route.

**Table 3.2 Summary of GHS Human Health Hazard Classifications for Copper Massive and Justification**

Endpoint	GHS Classification	Justification
Specific Target Organ Toxicity – Repeated Exposure	Not Classified	No subchronic or chronic toxicity data are available for copper massive. Therefore, data available for other copper substances (copper sulfate and copper hydroxide) were used in the hazard assessment. High-quality data on oral toxicity <i>via</i> repeated exposure for copper sulfate are available in the CSR (ECI, 2018a). Only one dermal repeated-dose study of copper compounds and copper-containing substances was identified (a study of copper hydroxide; Paynter, 1965, as cited in ANSES, 2017). Regarding inhalation exposure, the particle size of copper massive is >1 µm, and therefore, these particles are not respirable and pose no specific target organ toxicity hazard <i>via</i> the inhalation exposure route. Copper massive is not classified as a STOT – RE hazard under the GHS based on a lack of target organ effects after repeated oral exposure to copper sulfate at levels <100 mg/kg-bw per day (Hébert, 1993, as cited in ECI, 2018a) or repeated dermal exposure to copper hydroxide at <200 mg/kg-bw per day (Paynter, 1965, as cited in ANSES, 2017) (the GHS guidance cut-off values for STOT – RE hazard classification for oral and dermal exposures, respectively).
Aspiration Hazard	Not Classified	Not applicable to copper metal, because aspiration hazard is only applicable to hydrocarbons, ketones, and alcohols.

## Notes:

bw = Body Weight; CSR = Chemical Safety Report for Copper; LC<sub>50</sub> = Median Lethal Concentration; LD<sub>50</sub> = Median Lethal Dose; LOAEC = Lowest Observed Adverse Effect Concentration; LOAEL = Lowest Observed Adverse Effect Level; STOT – RE = Specific Target Organ Toxicity – Repeated Exposure; STOT – SE = Specific Target Organ Toxicity – Single Exposure. GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

## 3.2 Copper Powder

Copper powder does not meet the criteria for classification as hazardous under the GHS for any human health hazards, as detailed for each endpoint below.

An *in vitro* bioaccessibility study of copper powder in artificial gastric fluid (conducted in accordance with ASTM D5517-07) demonstrated that the solubility of copper powder is relatively low – the release of copper ions from copper powder in artificial gastric fluid was 1.1-7.3% of its total potential release (Rodriguez *et al.*, 2010, as cited in ECI, 2018a; see Table 3.7). Table 3.3 presents the GHS human health classifications for copper powder and a summary of the justification for each classification.

**Table 3.3 Summary of GHS Human Health Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Acute Oral Toxicity	Not Classified	No acute oral toxicity data are available for copper powder. For copper powder and other copper compounds, the common functional moiety is the copper ion. The difference between the release of copper ions from copper powder compared to other copper compounds with reliable toxicological data was used to infer the toxicity of copper powder. Specifically, an LD <sub>50</sub> value for copper powder was predicted by extrapolating the relationship between bioaccessibility and toxicity measured for various other copper compounds. The predicted LD <sub>50</sub> for copper powder ranges from 4,357-8,107 mg/kg (ECI, 2018a). The cut-off oral LD <sub>50</sub> value for GHS classification is 2,000 mg/kg-bw ( <i>i.e.</i> , substances with LD <sub>50</sub> values above 2,000 mg/kg-bw are generally not classified as acute oral toxicants under the GHS). Therefore, copper powder does not require classification as an acute oral toxicity hazard under the GHS.
Acute Dermal Toxicity	Not Classified	No acute dermal toxicity data are available for copper powder. Therefore, high-quality studies of copper oxide, copper sulfate, and coated copper flakes, which have a similar or higher solubility in water (and are therefore assumed to be more bioavailable) and greater bioaccessibility in artificial gastric fluid than copper powder, were used for the hazard assessment of copper powder. These studies show that these copper compounds induce low acute toxicity <i>via</i> the dermal exposure route ( <i>i.e.</i> , LD <sub>50</sub> values >2,000 mg/kg-bw), which is consistent with the low expected dermal penetration of copper ions, the toxic moiety of copper substances. The cut-off dermal LD <sub>50</sub> for GHS classification is 2,000 mg/kg-bw ( <i>i.e.</i> , substances with LD <sub>50</sub> values above 2,000 mg/kg-bw are generally not classified as acute dermal toxicants under the GHS). Therefore, copper powder is not classified as an acute dermal toxicity hazard based on LD <sub>50</sub> values >2,000 mg/kg-bw in rats in studies of copper oxide (Sanders, 2002b, as cited in ECI, 2018a), copper sulfate (Lhertier, 1993, as cited in ECI, 2018a), and coated copper flakes (Sanders, 2001b, as cited in ECI, 2018a).

**Table 3.3 Summary of GHS Human Health Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Acute Inhalation Toxicity	Not Classified	No acute inhalation data are available for copper powder. Therefore, acute inhalation data for dicopper oxide, copper oxychloride, copper sulfate, and coated copper flakes (Greenough and McDonald, 1985; Blagen, 2001; Wesson, 2003; Holbert, 1994, all as cited in ECI, 2008; Wesson, 2001, as cited in ECI, 2018a; LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, 2011) were used for the hazard assessment of copper powder. Acute inhalation toxicity is largely determined by a substance's particle size and solubility (ECI, 2018a). The copper particles in the substances tested in these studies are generally much smaller than those of copper powder ( <i>i.e.</i> , 1.64-5.1 $\mu\text{m}$ versus 10-1,000 $\mu\text{m}$ ), and therefore more easily respirable/soluble. The particle size of copper powder has been demonstrated to be primarily >10 $\mu\text{m}$ (EBRC Consulting, 2005; Liipo <i>et al.</i> , 2010, as cited in ECI, 2018a). Therefore, considering the WoE for other copper compounds and the particle size distribution of copper powder, copper powder is not classified as an acute inhalation toxicity hazard under the GHS.
Skin Corrosion/Irritation	Not Classified	No skin irritation data are available for copper powder. Therefore, relatively recent, high-quality studies of copper oxide and coated copper flakes, which have low solubility in water, similar to copper powder, were used for the hazard assessment of copper powder. GHS hazard classification for skin irritation is warranted when mean Draize scores (for erythema or edema) meet or exceed 1.5 in at least two of three test animals (UN, 2017). Therefore, copper powder is not classified as a skin irritant under the GHS based on the negative results (Draize scores = 0) of reliable studies of copper oxide and coated copper flakes in rabbits (Sanders, 2002c, as cited in ECI, 2018a; Sanders, 2001a, as cited in ECHA, 2018a).

**Table 3.3 Summary of GHS Human Health Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Serious Eye Damage/ Eye Irritation	Not Classified	<p>No eye irritation data are available for copper powder. Therefore, data for copper oxide were used for the hazard assessment of copper powder. Copper oxide was considered the most appropriate surrogate for copper powder based on its low water solubility and lack of physical properties that could contribute to an eye irritation reaction (<i>e.g.</i>, coated copper flakes' blade-type edges). In addition, a high-quality guideline study (that reported test item purity) was available for copper oxide. Copper powder is not classified as an eye irritant under the GHS based on the negative results of a study of rabbits administered copper oxide (Sanders, 2002, as cited in OECD, 2010) and the generally negative results of several unpublished animal studies of other copper compounds. The mean Draize scores (average of readings from 24, 48, and 72 hours) for cornea opacity were 0, 0, and 1 for the three test animals. Mean scores for conjunctival redness and chemosis were 0.3, 0.3, and 1.7 and 0, 0, and 1.3, respectively. Mean scores for iris congestion were 0, 0, and 0.7. The minimum mean Draize scores for eye irritation hazard classification (average of the mean scores at 24, 48, and 72 hours post-exposure) are 1 for corneal opacity and iritis and 2 for conjunctival redness/edema (UN, 2017). In addition, these effects must be observed in two of three animals. Thus, copper oxide did not meet the hazard classification criteria to be considered mildly irritating to the eyes (Category 2B, the lowest hazard category for eye irritation; UN, 2017).</p> <p>In addition, several unpublished animal studies with less-soluble copper compounds (<i>e.g.</i>, copper oxide and copper dioxide) generally indicate they are not classified as eye irritants under the GHS, while copper sulfate, a more-soluble compound, is classified as an eye irritant (ECI, 2008).</p>
Respiratory or Skin Sensitization	Not Classified	<p>No respiratory sensitization data are available for copper powder or other copper compounds. Therefore, there is no basis for classifying copper powder as a respiratory sensitization hazard under the GHS.</p> <p>No skin sensitization data are available for copper powder. Therefore, a reliable guideline study on copper oxide (Sanders, 2002b, as cited in ECI, 2018a), which has low solubility and anticipated low dermal penetration, similar to copper powder, was used for the hazard assessment of copper powder. Based on the results of this study, copper powder is not classified as a skin sensitization hazard under the GHS. Supporting unpublished animal studies and some evidence in humans indicate that copper substances are generally not skin sensitizers (ANSES, 2013; ECI, 2008).</p>

**Table 3.3 Summary of GHS Human Health Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Germ Cell Mutagenicity	Not Classified	No mutagenicity or genotoxicity data are available for copper powder. Therefore, studies of copper sulfate were used for read-across to copper powder. Using a surrogate copper compound with higher solubility in water and artificial biological fluids (e.g., copper sulfate) for read-across to copper powder is conservative, because the availability of copper ions (considered to be the toxic moiety of copper substances) for uptake is expected to be higher for the surrogate than for copper powder. Copper powder is thus not classified as a germ cell mutagenicity hazard under the GHS based on negative results from guideline <i>in vitro</i> and <i>in vivo</i> genotoxicity studies of copper sulfate (Ward, 1994; Riley, 1994, both as cited in ECI, 2018a).
Carcinogenicity	Not Classified	No carcinogenicity data are available for copper powder, but relevant chronic animal studies of other copper substances, primarily copper sulfate, are available. Therefore, studies of copper sulfate were used for read-across to copper powder. Using data from a surrogate copper compound with higher solubility in water and artificial biological fluids (e.g., copper sulfate) for read-across to copper powder is conservative, because the availability of copper ions (considered to be the toxic moiety of copper substances) for uptake is expected to be higher for the surrogate than for copper powder. Copper powder is thus not classified as a carcinogenicity hazard based on negative findings from rodent carcinogenicity studies of copper sulfate (Carlton and Price, 1973; Burki and Okita, 1969; Harrison <i>et al.</i> , 1954, all as cited in ANSES, 2017) and supported by evidence in humans that indicates copper is not carcinogenic (ANSES, 2017).



**Table 3.3 Summary of GHS Human Health Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Reproductive Toxicity	Not Classified	No reproductive or developmental toxicity data are available for copper powder, but reliable reproductive/developmental animal studies are available for copper sulfate and copper chloride. Therefore, studies of copper sulfate and copper chloride were used for read-across to copper powder. Using data from surrogate copper compounds with higher solubility in water and artificial biological fluids (e.g., copper sulfate and copper chloride) for read-across to copper powder is conservative, because the availability of copper ions (considered to be the toxic moiety of copper substances) for uptake is expected to be higher for the surrogate than for copper powder. Copper powder is thus not classified as a reproductive toxicity hazard under the GHS based on a lack of reproductive and developmental toxicity in a study in rats administered copper sulfate (Mylchreest, 2005, as cited in ECI, 2018a) and supported by a reproductive/developmental screening test in rats administered copper chloride (Chung <i>et al.</i> , 2008, as cited in ECI, 2018a).
Specific Target Organ Toxicity – Single Exposure	Not Classified	Because no single-exposure or acute toxicity data are available for copper powder, the high-quality animal studies that are available for this endpoint, including studies of copper oxide (Sanders, 2002a,b, both as cited in ECI, 2018a), dicopper oxide (Greenough and McDonald, 1985; Blagen, 2001, both as cited in ECI, 2008), copper sulfate (Lehritier, 1993, 1994, both as cited in ECHA, 2018a; Holbert, 1994; Wesson, 2003, both as cited in ECI, 2008), and coated copper flakes (Sanders, 2001b, as cited in ECHA, 2018a), were used for the hazard assessment of copper powder. The results of these studies were supported by relevant human data for copper sulfate (Araya <i>et al.</i> , 2001, 2003, both as cited in ECI, 2018a; ECHA, 2014a). The GHS guidance cut-off values (LOAEL/LOAEC) for STOT – SE hazard classification are 2,000 mg/kg-bw for oral and dermal exposures and 5 mg/L for inhalation exposure (for dust/mist/fume) (UN, 2017). Copper powder is thus not classified as a STOT – SE hazard under the GHS based on a lack of target organ effects in animals after acute oral, dermal, and inhalation exposures to the aforementioned surrogate copper compounds at levels requiring GHS classification (Sanders, 2002a,b; Araya <i>et al.</i> , 2001, 2003, all as cited in ECI, 2018a; Greenough and McDonald, 1985; Blagen, 2001; Holbert, 1994; Wesson 2003, all as cited in ECI, 2008).

**Table 3.3 Summary of GHS Human Health Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Specific Target Organ Toxicity – Repeated Exposure	Not Classified	No subchronic or chronic toxicity data are available for copper powder. Therefore, the data that are available for other copper substances (copper sulfate, copper hydroxide, and dicopper oxide) were used for the hazard assessment of copper powder. High-quality data on oral toxicity <i>via</i> repeated exposure for copper sulfate are available in the CSR (ECI, 2018a). Only one dermal repeated-dose study was identified for any copper compounds and copper-containing substances (a study of copper hydroxide; Paynter, 1965, as cited in ANSES, 2017). An available high-quality study of inhalation exposure to dicopper oxide in rats found no significant irreversible effects up to 2.0 mg/m <sup>3</sup> (Kirkpatrick, 2010, as cited in ANSES, 2017). The cut-off in the GHS guidance for STOT – RE hazard classification for the oral, dermal, and inhalation routes of exposure are 100 mg/kg-day (LOAEL), 200 mg/kg-day (LOAEL), and 0.2 mg/m <sup>3</sup> (LOAEC), respectively (UN, 2017). Copper powder is thus not classified as a STOT – RE hazard under the GHS, based on a lack of target organ effects after repeated oral exposure to copper sulfate at levels <100 mg/kg-bw/day (Hébert, 1993, as cited in ECI, 2018a), dermal exposure to copper hydroxide at <200 mg/kg-bw/day (Paynter, 1965, as cited in ANSES, 2017), and inhalation exposure to dicopper oxide <0.2 mg/m <sup>3</sup> (Kirkpatrick, 2010, as cited in ANSES, 2017).
Aspiration Hazard	Not Classified	Not applicable to copper metal, because aspiration hazard is only applicable to hydrocarbons, ketones, and alcohols.

Notes:

bw = Body Weight; CSR = Chemical Safety Report for Copper; LC<sub>50</sub> = Median Lethal Concentration; LD<sub>50</sub> = Median Lethal Dose; LOAEC = Lowest Observed Adverse Effect Concentration; LOAEL = Lowest Observed Adverse Effect Level; STOT – RE = Specific Target Organ Toxicity – Repeated Exposure; STOT – SE = Specific Target Organ Toxicity – Single Exposure; WoE = Weight of the Evidence.

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

### 3.3 Coated Copper Flakes

Copper flakes coated with aliphatic acid (hereafter "coated copper flakes") are reddish, metallic copper flakes characterized by a surface coating (*e.g.*, stearic acid, zinc stearate), high surface area (2,900 mm<sup>2</sup>/mg), and a particle size of 5-100 µm (ECI, 2018a). Coated copper flakes are an active substance used as a biocidal and plant protection product (ANSES, 2013). Due to the aliphatic acid coating and high bioavailability, coated copper flakes are assessed independently herein from other forms of copper metal.

Coated copper flakes are composed of copper (≥93 to ≤98% weight/weight), impurities such as dicopper oxide (<3%), and additives such as stearic acid (<3%) (Table 3.4; ECI, 2018a). Aliphatic acids, such as stearic acid, are "added for the production of coated copper flakes, to stabilize the copper flake in small particle sizes with higher surface area (needed for specific niche applications – biocides and pigments)" (OECD, 2014). Stearates such as zinc stearate can also be used for coating copper flakes (ECHA, 2018a).

**Table 3.4 Typical Composition of Coated Copper Flakes**

Chemical Constituents	CAS#	Percentage
Copper	7440-50-8	≥93% - ≤98% w/w
Dicopper Oxide	1317-39-1	<3%
Stearic Acid	57-11-4	<3%

Notes:

CAS# = Chemical Abstracts Service Registration Number; w/w = Weight per Weight.

Source: Chemical Safety Report for Copper (ECI, 2018a).

Table 3.5 presents the GHS human health classifications for coated copper flakes and a summary of the justification for each classification.

**Table 3.5 Summary of GHS Human Health Hazard Classifications for Coated Copper Flakes and Justification**

Endpoint	GHS Classification	Justification
Acute Oral Toxicity	Category 4	Coated copper flakes are classified as an Acute Oral Toxicity Category 4 hazard based on an estimated LD <sub>50</sub> between 300 and 500 mg/kg-bw (Sanders, 2001b, as cited in ECHA, 2018a). The GHS classification criterion for Acute Oral Toxicity Category 4 is an LD <sub>50</sub> between 300 and 2,000 mg/kg-bw (UN, 2017). Because the estimated LD <sub>50</sub> range falls within the range for this classification category, coated copper flakes are classified as an Acute Oral Toxicity Category 4 hazard under the GHS.

**Table 3.5 Summary of GHS Human Health Hazard Classifications for Coated Copper Flakes and Justification**

Endpoint	GHS Classification	Justification
Acute Dermal Toxicity	Not Classified	Coated copper flakes are not classified as an acute dermal toxicant based on an LD <sub>50</sub> >2,000 mg/kg-bw in rats. An OECD Test Guideline 402 study of coated copper flakes in rats found no mortality or signs of systemic toxicity at test concentrations up to 2,000 mg/kg-bw (Sanders, 2001b, as cited in ECHA, 2018a). The low acute dermal toxicity for coated copper flakes observed in this study is consistent with the low expected dermal penetration of copper ions, the toxic moiety of copper substances. The GHS cut-off dermal LD <sub>50</sub> value for acute dermal toxicity classification is 2,000 mg/kg-bw ( <i>i.e.</i> , substances with LD <sub>50</sub> values above 2,000 mg/kg-bw are generally not classified as acute dermal toxicity hazards under GHS). Therefore, based on the fact that no mortality or signs of systemic toxicity have been observed for coated copper flakes at doses up to 2,000 mg/kg-bw, coated copper flakes are not classified as an acute dermal toxicity hazard under the GHS.
Acute Inhalation Toxicity	Category 3	Coated copper flakes are conservatively classified as an Acute Inhalation Toxicity Category 3 hazard based on an LC <sub>50</sub> value of 1.03 mg/L. The GHS classification criterion for Acute Inhalation Toxicity Category 3 (for dust/mist/fume) is an LC <sub>50</sub> value between 0.5 and 1 mg/L (inclusive). While there is evidence from a reliable study (LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, 2011) that supports no GHS classification for coated copper flakes for this endpoint ( <i>i.e.</i> , LC <sub>50</sub> >5 mg/L), coated copper flakes are conservatively classified as an Acute Inhalation Toxicity Category 3 hazard under the GHS based on an LC <sub>50</sub> of 1.03 mg/L in rats (Wesson, 2001, as cited in ECI, 2018a).
Skin Corrosion/Irritation	Not Classified	Coated copper flakes are not classified a skin irritant based on the negative results of an OECD Test Guideline 404, GLP-compliant rabbit study of coated copper flakes (Sanders, 2001a, as cited in ECHA, 2018a), supported by other animals studies that indicate copper substances are generally not skin irritants (ECI, 2008). GHS hazard classification for skin irritation is warranted when mean Draize scores (for erythema or edema) meet or exceed 1.5 in at least two of three test animals (UN, 2017). In Sanders (2001a, as cited in ECHA, 2018a), no erythema or edema (Draize scores = 0) were observed in rabbits exposed to coated copper flakes under semi-occlusive conditions for 4 hours. Therefore, coated copper flakes are not classified as a skin corrosion/irritation hazard.

**Table 3.5 Summary of GHS Human Health Hazard Classifications for Coated Copper Flakes and Justification**

Endpoint	GHS Classification	Justification
Serious Eye Damage/ Eye Irritation	Category 2A	Coated copper flakes are classified as a Category 2A eye irritant under the GHS based on the positive results of an OECD Test Guideline 405 study in rabbits conducted with coated copper flakes (Sanders, 2001d, as cited in ECI, 2018a). Coated copper flakes induced a slight eye irritation response in this study, with all effects fully reversed within 14 days. A substance is classified as a Category 2A eye irritant if mean Draize scores in at least two of three tested animals are $\geq 1$ for corneal opacity, $\geq 1$ for iritis, $\geq 2$ for conjunctival redness, and/or $\geq 2$ for conjunctival edema, and if the effect or effects fully reverse within 21 days (UN, 2017). Category 2B is determined by the same mean Draize score criteria, but effects must be fully reversible within 7 days (UN, 2017). In Sanders (2001d, as cited in ECI, 2018a), the mean Draize scores for corneal opacity met the GHS classification criteria in two of the three study animals, but the criteria were not met for any other eye irritation effect. In addition, all the effects observed in this study were fully reversible within 14 days. Therefore, coated copper flakes are classified as an Eye Irritation Category 2A hazard under the GHS.
Respiratory or Skin Sensitization	Not Classified	<p>No respiratory sensitization data are available for coated copper flakes or other copper compounds. Therefore, there is no basis for classifying coated copper flakes as a respiratory sensitization hazard under the GHS.</p> <p>Coated copper flakes are not classified as a skin sensitizer based on a lack of skin sensitization in guinea pigs (Sanders <i>et al.</i>, 2001e, as cited in ECHA, 2018a), supported by several unpublished animal studies as well as evidence in humans indicating that copper substances are generally not skin sensitizers (ANSES, 2013; ECI, 2008). GHS hazard classification for skin sensitization based on a guinea pig maximization test necessitates positive sensitization reactions in at least 30% of test animals (UN, 2017). None of the test animals in the identified guinea pig study showed positive sensitization reactions following challenge (Sanders <i>et al.</i>, 2001e, as cited in ECHA, 2018a). Therefore, coated copper flakes are not classified as a skin sensitization hazard under the GHS.</p>
Germ Cell Mutagenicity	Not Classified	Because no mutagenicity or genotoxicity data are available for coated copper flakes, the high-quality studies of copper sulfate that are available were used for the hazard assessment of coated copper flakes. Although genotoxicity studies of other copper compounds, particularly copper chloride and copper acetate, are available, these studies alone are not reliable enough to use for risk assessment or for determining GHS hazard classifications (ECI, 2008). Coated copper flakes are thus not classified as a germ cell mutagenicity hazard under the GHS based on the negative results from guideline <i>in vitro</i> and <i>in vivo</i> genotoxicity studies of copper sulfate (Ward, 1994; Riley, 1994, both as cited in ECI, 2018a), supported by similar negative findings for copper chloride (ECI, 2008).

**Table 3.5 Summary of GHS Human Health Hazard Classifications for Coated Copper Flakes and Justification**

Endpoint	GHS Classification	Justification
Carcinogenicity	Not Classified	No carcinogenicity data are available for coated copper flakes, but relevant chronic animal studies of other copper substances, primarily soluble copper sulfate, are available. Therefore, studies of copper sulfate were used for read-across to coated copper flakes. Coated copper flakes are not classified as a carcinogenicity hazard under the GHS based on negative findings in rodent carcinogenicity studies with copper sulfate (Carlton and Price, 1973; Burki and Okita, 1969; Harrison <i>et al.</i> , 1954, all as cited in ANSES, 2017) and supported by evidence in humans that indicate copper is not carcinogenic (ANSES, 2017).
Reproductive Toxicity	Not Classified	Because no reproductive or developmental toxicity data were identified for coated copper flakes specifically, the high-quality data for this endpoint that are available for copper sulfate and copper chloride were used for the hazard assessment of coated copper flakes. Coated copper flakes are not classified as a reproductive toxicity hazard under the GHS based on a lack of reproductive and developmental toxicity in a study in rats administered copper sulfate (Mylchreest, 2005, as cited in ECI, 2018a) and supported by a reproductive/developmental screening test in rats administered copper chloride (Chung <i>et al.</i> , 2008, as cited in ECI, 2018a).
Specific Target Organ Toxicity – Single Exposure	Not Classified	Coated copper flakes are not classified as a STOT – SE hazard under the GHS based on a lack of organ-specific effects at moderate exposure levels in acute toxicity studies in rats exposed to coated copper flakes <i>via</i> the oral, dermal, and inhalation exposure routes (Sanders, 2001b, 2001d; Wessen, 2001, all as cited in ANSES, 2013; LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, 2011). The results of these studies were supported by relevant human data for copper sulfate (Araya <i>et al.</i> , 2001, 2003, both as cited in ECI, 2018a; ECHA, 2014a). The observed effects in all these studies were largely considered to be non-specific, unspecified signs of general acute toxicity.

**Table 3.5 Summary of GHS Human Health Hazard Classifications for Coated Copper Flakes and Justification**

Endpoint	GHS Classification	Justification
Specific Target Organ Toxicity – Repeated Exposure	Not Classified	No subchronic or chronic toxicity data are available for coated copper flakes. Therefore, the reliable data for this endpoint that are available for copper sulfate, copper hydroxide, and dicopper oxide were used for the hazard assessment of coated copper flakes. High-quality data on oral toxicity <i>via</i> repeated exposure for copper sulfate are available in the CSR (ECI, 2018a). Only one dermal repeated-dose study was identified for copper compounds and copper-containing substances (a study of copper hydroxide; Paynter, 1965, as cited in ANSES, 2017). A high-quality study of inhalation exposure to dicopper oxide in rats found no significant irreversible effects up to 2.0 mg/m <sup>3</sup> (Kirkpatrick, 2010, as cited in ANSES, 2017). The cut-off in the GHS guidance for STOT – RE hazard classification for the oral, dermal, and inhalation routes of exposure are 100 mg/kg-day (LOAEL), 200 mg/kg-day (LOAEL), and 0.2 mg/m <sup>3</sup> (LOAEC), respectively (UN, 2017). Coated copper flakes are thus not classified as a STOT – RE hazard under the GHS based on a lack of target organ effects after repeated oral exposure to soluble copper sulfate at levels <100 mg/kg-bw per day (Hébert, 1993, as cited in ECI, 2018a), dermal exposure to copper hydroxide at <200 mg/kg-bw per day (Paynter, 1965, as cited in ANSES, 2017), and inhalation exposure to dicopper oxide <0.2 mg/m <sup>3</sup> (Kirkpatrick, 2010, as cited in ANSES, 2017).
Aspiration Hazard	Not Classified	Not applicable to copper metal, because aspiration hazard is only applicable to hydrocarbons, ketones, and alcohols.

Notes:

bw = Body Weight; CSR = Chemical Safety Report for Copper; LC<sub>50</sub> = Median Lethal Concentration; LD<sub>50</sub> = Median Lethal Dose; LOAEC = Lowest Observed Adverse Effect Concentration; LOAEL = Lowest Observed Adverse Effect Level; OECD = Organisation for Economic Co-operation and Development; STOT – RE = Specific Target Organ Toxicity – Repeated Exposure; STOT – SE = Specific Target Organ Toxicity – Single Exposure.

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

### 3.4 Summary of GHS Human Health Hazard Classifications

The following health hazard classifications are based on the principals and criteria presented in the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017). No health hazards are assigned to copper massive or copper powder. Coated copper flakes, which are chemically and toxicologically distinct from the other forms of copper assessed herein, are assigned the following human health hazards under the GHS: Acute Oral Toxicity Category 4, Acute Inhalation Toxicity Category 3, and Eye Irritation Category 2A. Table 3.6 summarizes these hazard classifications and presents the GHS hazard statement codes, when applicable.

**Table 3.6 Summary of GHS Human Health Hazard Classifications for Copper Metal Forms**

Copper Metal Form	GHS Hazard Classifications	GHS Hazard Statement Code
Copper Massive CAS: 7440-50-8, EC: 231-159-6	Not Classified	NA
Copper Powder CAS: 7440-50-8, EC: 231-159-6	Not Classified	NA
Coated Copper Flakes No CAS or EC numbers allocated	Acute Oral Toxicity Category 4	H302: Harmful if swallowed
	Acute Inhalation Toxicity Category 3	H331: Toxic if inhaled
	Eye Irritation Category 2A	H319: Causes serious eye irritation

Notes:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017); NA = Not Applicable.



## 4 GHS Environmental Hazard Classifications

For metals such as copper, the approach to classification for environmental hazards is presented in Annex 9 of the 7<sup>th</sup> Revised Edition of the GHS guidance document (UN, 2017). The environmental hazard assessment described herein follows the principles and criteria presented within Annex 9, specifically Section 7.5 ("Application of classification criteria to metals and metal compounds"; UN, 2017). The GHS environmental hazard endpoints and basic elements for classifying environmental hazards under the GHS are presented in Table 4.1. Copper bioavailability, solubility, and ecotoxicity have been extensively studied in the literature, and these properties are discussed below. This discussion is applicable to copper metal in its various forms and was used to inform the classification of environmental hazards for copper massive, copper powder, and coated copper flakes according to the GHS system.

**Table 4.1 GHS Environmental Hazard Endpoints and Basic Elements**

Hazard Endpoint/Basic Element	Definition
<b>GHS Hazard Endpoints</b>	
Acute Aquatic Toxicity	" <i>Acute aquatic toxicity</i> means the intrinsic property of a substance to be injurious to an organism in a short-term aquatic exposure to that substance."  " <i>Short-term (acute) hazard</i> , for classification purposes, means the hazard of a chemical caused by its acute toxicity to an organism during short-term aquatic exposure to that chemical."
Chronic Aquatic Toxicity	" <i>Chronic aquatic toxicity</i> means the intrinsic property of a substance to cause adverse effects to aquatic organisms during aquatic exposures which are determined in relation to the life-cycle of the organism."  " <i>Long-term (chronic) hazard</i> , for classification purposes, means the hazard of a chemical caused by its chronic toxicity following long-term exposure in the aquatic environment."
Hazardous to the Ozone Layer	" <i>Ozone Depleting Potential (ODP)</i> is an integrative quantity, distinct for each halocarbon source species, that represents the extent of ozone depletion in the stratosphere expected from the halocarbon on a mass-for-mass basis relative to CFC-11. The formal definition of ODP is the ratio of integrated perturbations to total ozone, for a differential mass emission of a particular compound relative to an equal emission of CFC-11."
<b>Basic Elements<sup>1</sup></b>	
Bioavailability	" <i>Bioavailability</i> (or biological availability) means the extent to which a substance is taken up by an organism, and distributed to an area within the organism. It is dependent upon physico-chemical properties of the substance, anatomy and physiology of the organism, pharmacokinetics, and route of exposure. Availability is not a prerequisite for bioavailability."
Bioaccumulation	" <i>Bioaccumulation</i> means net result of uptake, transformation and elimination of a substance in an organism due to all routes of exposure (i.e. air, water, sediment/soil and food)."
Bioconcentration	" <i>Bioconcentration</i> means net result of uptake, transformation and elimination of a substance in an organism due to waterborne exposure."

**Table 4.1 GHS Environmental Hazard Endpoints and Basic Elements**

Hazard Endpoint/Basic Element	Definition
Removal/Partitioning from the Water Column	"Metals and metal compounds can undergo interactions with the media which affect the solubility of the metal ion, partitioning from the water column, and the species of metal ion that exists in the water column. In the water column, it is generally the dissolved metal ions which are of concern for toxicity. The interaction of the substance with the media may either increase or decrease the level of ions and hence toxicity. It is thus necessary to consider whether metal ions are likely to be formed from the substance and dissolve in the water, and if so whether they are formed rapidly enough to cause concern."

Notes:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals.

Source: UN (2017 [emphasis in original]).

(1) Basic elements are not GHS hazard endpoints but are essential to the classification process for environmental hazards.

## 4.1 Approach to GHS Environmental Hazard Classification

### 4.1.1 Aquatic Environment Hazards

The solubility and bioavailability of copper ions govern the ecotoxicological hazards of copper metal. A copper substance's toxicity is determined by the concentration of free copper ions in the substance as well as the environmental factors that influence their activity. Free ion activity, and, subsequently, copper toxicity, varies with water chemistry parameters such as pH, water hardness, and concentration of dissolved organic carbon (DOC) (ARCHE and ECI, 2018). Toxicity occurs because free copper ions disrupt the homeostasis of other essential ions, such as calcium and sodium; therefore, metal complexation and interaction at the site of action also influences toxicity, and these parameters are also considered when evaluating the ecotoxicity of copper and copper containing substances (ECI, 2018a).

To incorporate these variables, researchers developed a mechanistically based model called the Biotic Ligand Model (BLM) to describe copper bioavailability and toxicity to aquatic biota. The BLM simulates copper toxicity by assuming metal accumulation at the biological site of action, known as the biotic ligand (*e.g.*, the surface membrane of the gill, for fish), and is used to predict the toxicity of copper in various water chemistries by incorporating the concentration of the free copper ion as the toxic species, as well as the competition of other cations (*e.g.*,  $\text{Ca}^{2+}$ ) for binding at the biotic ligand (ECI, 2018a). BLMs have been developed for different trophic levels (fish, invertebrates, algae) using different methodologies. The 10 key water characteristic BLM inputs are: temperature, pH, DOC concentration, major cation ( $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Na}^+$ , and  $\text{K}^+$ ) concentrations, major anion ( $\text{Cl}^-$  and  $\text{SO}_4^{2-}$ ) concentrations, alkalinity, and water hardness. In general, greater water hardness, higher DOC concentration, and higher pH reduce copper's toxicity (ARCHE and ECI, 2018). Water chemistry parameters, particularly pH and DOC concentration, were considered in the development of ecotoxicity reference values (ERVs) for copper massive, copper powder, and coated copper flakes (ARCHE and ECI, 2018).

Although metallic copper is insoluble in water, it has the potential to gradually oxidize in surface waters during transformation (*i.e.*, the rate and extent to which a metal ion will react with media to transform into water-soluble forms) or dissolution (T/D). In general, a chemical's potential to present an ecological hazard is limited its solubility in water, and its rate of dissolution is not considered to be relevant to the determination of its intrinsic toxicity. However, for metals and metal compounds, the rate of T/D will essentially determine the concentration of dissolved metal ions in water and, therefore, the toxicity of the metal or metal compound. Determining GHS environmental hazard classifications for various forms of

copper metal is ultimately done by comparing the available aquatic toxicity data for copper ions and solubility data for specific forms of copper. In other words, GHS hazard classifications are determined by comparing the intrinsic toxicity of the copper ions to the rate and amount of ions that enter solution for each form of copper metal. This process is described further below.

#### 4.1.1.1 Ecotoxicity Reference Values

Toxicity is assessed using calculated ecotoxicity reference values (ERVs) based upon ecotoxicity data for soluble inorganic compounds to determine the toxicity of the metal ion to aquatic organisms. Ecotoxicity studies of soluble copper compounds (most often copper sulfate and copper chloride) have been combined into large datasets from which the final acute and chronic ERVs for copper are derived (ARCHE and ECI, 2016, 2018). The hazard classifications presented within this document rely upon the most recently updated ERVs developed by the European Copper Institute (ECI) (ARCHE and ECI, 2016, 2018), which were derived using the following approach.

- Retention of only high-quality studies (equivalent to standard guideline test methods, *e.g.*, OECD) and those that used standard test species (data for *C. dubia* were excluded);
- Calculation of the geometric mean of toxicity values for each test species and pH class combination with greater than four data points;
- Division by pH band (5.5-6.5, 6.51-7.5, 7.51-8.5), in accordance with the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017); and
- Consideration of both normalized (to DOC concentration) and non-normalized data in the ERV derivation. Non-normalized data were retained for both the acute and chronic ERV, because this approach resulted in the largest dataset. The normalized values indicated no strong bias due to the inclusion of the DOC concentration data in the dataset.

The ERVs (see Table 4.2) for copper are expressed as dissolved copper concentrations ( $\mu\text{g/L}$ ) required to achieve a median acute mortality or effect concentration ( $\text{L[E]C}_{50}$ ) or a chronic no observed effect concentration (NOEC) or 10% effect concentration ( $\text{EC}_{10}$ ). Complete details on the derivation of these ERVs can be found in the specific technical documents produced by the ECI (ARCHE and ECI, 2016, 2018; ECI, 2018b).

**Table 4.2 Acute and Chronic Ecotoxicity Reference Values (ERVs) for Copper**

pH Range	Acute ERV: $\text{L(E)C}_{50}$ ( $\mu\text{g copper/L}$ )	Chronic ERV: NOEC/ $\text{EC}_{10}$ ( $\mu\text{g copper/L}$ )
6 (5.5-6.5)	12	13
7 (6.51-7.5)	14	12
8 (7.51-8.5)	40	13

Notes:

$\text{EC}_{10}$  = 10% Effect Concentration;  $\text{L(E)C}_{50}$  = Median Acute Mortality or Effect Concentration; NOEC = No Observed Effect Concentration.

Source: ECI (2018b).

#### 4.1.1.2 Transformation/Dissolution Tests

T/D testing can determine the relationship between the concentration of metal ions released after a specified amount of time and the mass and surface area loadings of the tested metal form. Results from T/D tests show that the release of copper ions from various copper metal forms depends on the exposed surface area of the substance, such that a greater exposed surface area results in a greater release of copper ions.

Details on the available T/D studies for copper are provided in the CSR (ECI, 2018a). These studies were performed with several copper substances, experimental protocols, and loadings. The selection of the most appropriate T/D data for each copper metal form is outlined in the subsequent form-specific bioavailability sections of this document. To develop conservative GHS hazard classifications for copper massive and copper powder, the SSA for the smallest particle size for each form was used to convert the concentration of copper ions released per unit surface area ( $\mu\text{g}/\text{mm}^2$ ) to the concentration of copper ions released from the substance ( $\mu\text{g}/\text{L}$ ) at a mass loading rate of 1 mg/L. For coated copper flakes, the SSA used in this conversion was derived experimentally.

#### 4.1.1.3 Persistence and Degradability

Copper cannot be degraded, but it can be transformed between different phases, chemical species, and oxidation states. For metals, potential transformation of metal species to non-bioavailable forms is described by the term "rapid removal," instead of "degradability." Removal of soluble metal species from the water column can occur through several physical and chemical processes, such as complexation, precipitation, adsorption, and settling (ECI, 2018a). Similar to the criteria for organic species, a metal is considered rapidly removable if tests demonstrate a  $\geq 70\%$  reduction in soluble metal species within 28 days (UN, 2017). In evaluating rapid removal, it is important to consider numerous factors, especially the bioavailability of transformed species and the reversibility of the transformation processes (*e.g.*, remobilization from sediment or further transformation into bioavailable chemical species or oxidation states).

A thorough review of the relevant data, including some newly available evidence, indicates that copper can be considered rapidly removable from the water column (ECI, 2018a). The assessment of whether copper metal is considered rapidly removable was based on three lines of evidence: (1) the intrinsic properties of copper metal that drive partitioning and speciation to non-toxic species, (2) experimental evidence that quantifies the rate of copper removal under a range of environmental conditions, and (3) quantification of the change in copper speciation to less soluble, non-bioavailable forms (and the reversibility of these changes) under a range of environmental conditions. Studies for all three lines of evidence are summarized in an attachment to the CSR (ECI, 2018b). This report concludes:

In view of the newly available evidence... it can therefore be concluded that under most "environmentally relevant" conditions, more than 70% of dissolved copper is removed within 28 days. Copper is transformed to sulfide complexes (Cu-S) which are stable. Remobilisation of Cu to the water-column is not likely to occur. Copper is therefore considered rapidly removed, conceptually equivalent to "rapid degradation" for organic substances. (ECI, 2018b)

For the purpose of GHS hazard classification, this is analogous to copper being designated as a rapidly degradable substance (UN, 2017). The ecotoxicity hazard classifications for all the copper forms evaluated in this document are based on the assumption that copper metal *is* rapidly removable from the water column. The concept of a metal being "rapidly removable" from the water column has not yet been accepted by all jurisdictions, nor has the conclusion that copper metal should be considered rapidly removable from the

water column for the purpose of GHS hazard classification. Various international bodies are conducting ongoing discussions that aim to reach an agreed-upon approach to assessing the persistence and degradability of metals, based on the best available science, for the purposes of classifying their environmental hazards.

#### **4.1.1.4 Bioaccumulation Potential**

Due to homeostatic regulation, the "bioaccumulative" criterion is not applicable to essential metals, and this endpoint should be evaluated on a case-by-case basis using expert judgement (UN, 2017). In other words, partition coefficients ( $\log P_{ow}$ ) and bioconcentration/bioaccumulation factors (BCFs/BAFs) have no ecotoxicological significance for essential metals, so alternative types of data should be considered to evaluate the potential bioaccumulation of these substances. Importantly, a review of the literature demonstrates that copper is not biomagnified in aquatic or terrestrial ecosystems (ECHA, 2018a). As summarized in the CLH Report for Granulated Copper, the data clearly demonstrate that:

(1) copper is an essential nutrient for all living organisms, and (2) copper ions are homeostatically controlled in all organisms, and the control efficiencies increase with trophic chain. As a consequence, (1) copper BCF/BAF values decrease with increasing exposure concentrations (water and food), vary depending on nutritional needs (seasonal, life stage, species-dependent) and on internal detoxification mechanisms; (2) copper BMFs values are  $<1$ ; and (3) water-borne exposure (not diet-borne exposure) is the critical exposure route for copper toxicity. (ANSES, 2017)

The European Union Voluntary Risk Assessment Report for Copper also provides details on the above lines of evidence (ECI, 2008). The ecotoxicity hazard classifications for all the copper forms evaluated in this document are based on the assumption that copper metal is not bioaccumulative.

#### **4.1.1.5 GHS Classification for Metals**

The GHS hazard criteria for acute and chronic aquatic toxicity are presented in Annex 9 (Section 9.7.5) and outlined in Figure A9.7.1 ("Classification Strategy for Metals and Metal Compounds") in the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017). The final determination of a metal's acute and chronic aquatic hazards under the GHS is made by comparing the concentration of copper ions released from T/D testing of that substance (at specific mass loading rates, expressed in mg/L) to the ERVs for copper ions. If the concentration of metal ions released in the T/D test meets or exceeds the ERV, then the substance is classified into the hazard category that corresponds to the mass loading rate.

For acute aquatic toxicity, metals are classified as Category 1, 2, or 3 hazards based on whether the release of metal ions from T/D testing exceeds the acute ERV at low (1 mg/L), medium (10 mg/L), and high (100 mg/L) mass loading rates, respectively (UN, 2017). For example, if the results of acute T/D testing (7 days) of a copper compound at a mass loading rate of 1 mg/L exceed the acute ERV for copper, the compound is classified as an Acute Aquatic Toxicity Category 1 hazard. Based on the assumption of a generally linear association between mass loading and release of metal ions, the release of ions at a mass loading of 1 mg/L can be extrapolated to higher mass loading rates associated with Acute Aquatic Toxicity Categories 2 and 3. In addition, because both T/D testing for metals and metals' ecotoxicity depend on pH, only values from the same pH band are compared, using the pH band from the most conservative (*i.e.*, highest) T/D testing result.

For chronic aquatic toxicity, metals are classified as Category 1, 2, or 3 hazards based on whether the release of metal ions from T/D testing exceeds the chronic ERV at low (0.01 mg/L), medium (0.1 mg/L), and high (1 mg/L) mass loading rates, respectively; whether a metal is considered bioaccumulative and rapidly removable from the water column; as well as whether there are adequate chronic toxicity data available for the metal of interest (UN, 2017). The GHS guidance does not explicitly specify hazard classification criteria for metals that are rapidly removable and non-bioaccumulative, so the chronic aquatic hazard classifications presented in this document relied on expert judgement to aid in the classification process. Specifically, in line with the logic present in Table 4.1.1(b)(ii) ("Rapidly degradable substances for which there are adequate toxicity data available") in the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017) and consistent with ECHA's "Guidance on the Application of the CLP Criteria" (ECHA, 2017), if a rapidly removable, non-bioaccumulative substance was categorized as acute aquatic toxicity hazard, the results of chronic T/D testing at the lower mass loading rates (0.01, 0.1, or 1 mg/L) were then compared to the chronic ERV to determine whether the substance met the hazard classification criteria for chronic aquatic toxicity. In essence, the chronic hazard classifications for rapidly removable and non-bioaccumulative metals are, in general, one or more categories lower compared to the acute hazard classification (*e.g.*, a metal that is an Acute Aquatic Toxicity Category 1 hazard would be a Chronic Aquatic Toxicity Category 2 or 3 hazard). Expert judgement should be applied in all cases. This interpretation of the GHS guidance is consistent with the ECHA CLP guidance on classification of metals (ECHA, 2017).

The alternative, more literal interpretation of the GHS guidance is to not classify a metal for chronic aquatic toxicity hazard if it is both rapidly removable from the water column and non-bioaccumulative, regardless of the metal's assigned acute toxicity hazard or chronic T/D testing results. In this case, metals determined to be both rapidly removed from the water column and non-bioaccumulative would never carry a chronic aquatic toxicity hazard. This second interpretation is not consistent with current best practices in the field and was therefore not used for GHS hazard classification of the copper metal forms in this document.

In addition, substances with an Acute Aquatic Toxicity 1 or Chronic Aquatic Toxicity 1 hazard classification with acute ERVs well below 1 mg/L and chronic ERVs well below 0.1 mg/L (if non-rapidly degradable) and 0.01 mg/L (if rapidly degradable) may be assigned a multiplying factor (M factor) to account for the high toxicity of such substances by increasing the weight given to these substances during the mixture classification process (UN, 2017). The value of the M factor is inversely proportional to the acute or chronic ERV, because more-toxic substances are given more weight and assigned higher M factors (see Table 4.3). When deriving M factors in the hazard assessment of the copper metal forms evaluated herein, the effect concentrations (*e.g.*, L[E]C<sub>50</sub>) for copper ions were adjusted to account for the solubility of each copper metal form.

**Table 4.3 Multiplying Factors for Highly Toxic Ingredients of Mixtures**

Acute Aquatic Toxicity L(E)C <sub>50</sub> (mg/L)	M Factor	Chronic Aquatic Toxicity	M Factor	
		NOEC (mg/L)	Non-rapidly Degradable	Rapidly Degradable
0.1 < L(E)C <sub>50</sub> ≤ 1.0	1	0.01 < NOEC ≤ 0.1	1	–
0.01 < L(E)C <sub>50</sub> ≤ 0.1	10	0.001 < NOEC ≤ 0.01	10	1
0.001 < L(E)C <sub>50</sub> ≤ 0.01	100	0.0001 < NOEC ≤ 0.001	100	10
0.0001 < L(E)C <sub>50</sub> ≤ 0.001	1,000	0.00001 < NOEC ≤ 0.0001	1,000	100
(continue in factor 10 intervals)		(continue in factor 10 intervals)		

Notes:

L(E)C<sub>50</sub> = Median Acute Mortality or Effect Concentration; M Factor = Multiplying Factor; NOEC = No Observed Effect Concentration.

Table adapted from Table 4.1.5 of the GHS guidance (UN, 2017).

It is important to reiterate that the GHS guidance for assessing the chronic aquatic toxicity of metals is vague, leaving room for interpretation. This is especially true in the case of metals, such as copper, that are determined to be both rapidly removable from the water column and non-bioaccumulative. As previously mentioned, in the absence of clear and specific direction for hazard classification under the GHS, this assessment relied on expert judgement and the classification strategies presented in other reputable classification schemes (*e.g.*, the ECHA CLP scheme; ECHA, 2017).

There are some further differences between the GHS and ECHA CLP classification schemes. One important difference is that the GHS includes Acute Aquatic Toxicity Categories 1, 2, and 3, while the ECHA CLP scheme only includes Category 1 for acute aquatic toxicity hazard (UN, 2017; ECHA, 2017). In addition, some jurisdictions (*e.g.*, the United States and Canada) have not adopted hazard categories for any aquatic toxicity hazards, and others have adopted only select hazard categories. For example, the European Union and South Korean guidance on classifying acute aquatic toxicity hazards includes only Acute Aquatic Toxicity Category 1, so substances could not be classified as Acute Aquatic Toxicity Category 2 or 3 hazards in those jurisdictions. These differences between the various hazard classification schemes and how they are adopted (or not) by different jurisdictions may thus result in differing aquatic toxicity classifications for the same metal, even when the same data are evaluated.

#### 4.1.2 Ozone Layer Hazards

GHS hazard classification as a substance that is hazardous to the ozone layer requires that a substance either be listed in the Annexes of "The Montreal Protocol on Substances that Deplete the Ozone Layer" (UNEP, Ozone Secretariat, 2017) or contain a substance listed therein. Copper is not listed in the Annexes of the Montreal Protocol, and therefore, all three forms of copper metal (copper massive, copper powder, and coated copper flakes) evaluated in this report are not classified as hazardous to the ozone layer under the GHS.

## 4.2 Copper Massive

The SSA used for determining environmental hazard classifications for copper massive was 0.67 mm<sup>2</sup>/mg, based on a 1 mm-diameter sphere of copper massive with a density of 8.96 mg/mm<sup>3</sup> (Rodriguez *et al.*, 2012; Rodriguez *et al.*, 2017, as cited in ECI, 2018b). This is a reasonable "worst-case" (*i.e.*, finest) SSA for copper massive. Table 4.4 provides the GHS environmental hazard classifications for copper massive and a summary of the justification for each classification.

**Table 4.4 Summary of GHS Environmental Hazard Classifications for Copper Massive and Justification**

Endpoint	GHS Classification	Justification
Acute Aquatic Toxicity	Category 3	The concentration of copper ions released in 7-day T/D testing of copper massive measured at a mass loading rate of 100 mg/L and a pH of 6 (100 µg/L) exceeds the acute copper ERV at pH 6 (12 µg/L), so copper massive is classified as an Acute Aquatic Toxicity Category 3 hazard. Notably, this acute aquatic toxicity hazard category does not exist in the European Union's environmental hazard classification scheme (ECHA, 2017).

**Table 4.4 Summary of GHS Environmental Hazard Classifications for Copper Massive and Justification**

Endpoint	GHS Classification	Justification
Chronic Aquatic Toxicity	Not Classified	Copper massive is not classified as a chronic aquatic toxicity hazard under the GHS because (1) copper metal is considered both rapidly removable from the water column and non-bioaccumulative, and (2) the copper ion release from 28-day T/D testing of copper massive measured at a mass loading rate of 1 mg/L and a pH of 6 (3.4 µg/L) is lower than the chronic copper ERV at pH 6 (13 µg Cu/L).
Hazardous to the Ozone Layer	Not Classified	GHS hazard classification as a substance that is hazardous to the ozone layer requires that a substance either be listed in the Annexes of "The Montreal Protocol on Substances that Deplete the Ozone Layer" (UNEP, Ozone Secretariat, 2017) or contain a substance listed therein. Copper is not listed in the Annexes of the Montreal Protocol, and therefore copper massive is not classified as hazardous to the ozone layer under the GHS.

Notes:

ERV = Ecotoxicity Reference Value; T/D = Transformation/Dissolution.

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

ERVs are from ECI (2018b); T/D values are from Rodriguez *et al.* (2012) and Rodriguez *et al.* (2017, as cited in ECI, 2018b).

Rodriguez *et al.* (2007, as cited in ECI, 2018b) conducted preliminary testing of copper wire at surface loading concentrations ranging from 1.2-281 mm<sup>2</sup>/L. The data from this study demonstrate higher copper ion releases at lower pH as well as a positive linear relationship between copper ion releases and exposed surface area. For the 7-day test, the study found the average surface-specific release of copper ions to be 1.15 µg copper/mm<sup>2</sup> at a pH of 6. However, these data were not used for the hazard classification of copper massive due to high variability (likely due to particle abrasion) at the higher stirring rate (100 revolutions per minute [rpm]).

Rodriguez *et al.* (2012) and Rodriguez *et al.* (2017, as cited in ECI, 2018b) assessed the T/D of copper massive at 0.67 mm<sup>2</sup>/L surface loading, which is equivalent to a mass loading rate of 1 mg/L, in 7- and 28-day tests. The T/D data from these studies (presented in Table 4.5) were identified as the most reliable data for classification of copper massive for environmental hazards, assuming a copper massive particle with an SSA of 0.67 mm<sup>2</sup>/mg. To avoid abrasion, these studies were conducted with samples of copper massive embedded in epoxy resin. The data collected at a pH of 6 were retained to determine the environmental hazard classifications for copper massive, because these data resulted in the highest concentration of copper ions released from the test substance. As previously noted, for assessing acute hazards, the SSA for the smallest particle size for copper massive (*i.e.*, 0.67 mm<sup>2</sup>/mg) was used to convert the concentration of copper ions released per unit surface area (µg/mm<sup>2</sup>) to the concentration of copper ions released from the substance (µg/L) at a mass loading rate of 1 mg/L.

**Table 4.5 Results from the Transformation/Dissolution Test for Copper Massive**

Transformation/Dissolution Test		Release of Copper Ions Per Unit Surface Area (µg/mm <sup>2</sup> )			Release of Copper Ions from Copper Massive (µg copper/L)		
Mass Loading Rate (mg copper/L)	Time (Days)	pH 6	pH 7	pH 8	pH 6	pH 7	pH 8
1 mg/L	7 (acute)	1.5	0.6	<0.3	1.0	0.4	<0.2
10 mg/L <sup>1</sup>					<b>10</b>	<b>4.0</b>	<b>2</b>
100 mg/L <sup>1</sup>					<b>100</b>	<b>40</b>	<b>20</b>
1 mg/L	28 (chronic)	5.0	1.2	0.9	3.4	0.8	0.6

Notes:



Highlighted values are those that were used to determine the environmental hazard classifications for copper massive.

Sources: Rodriguez *et al.* (2012); Rodriguez *et al.* (2017, as cited in ECI, 2018b).

(1) Values in bold are extrapolations. A dilution factor of 10 and 100 was applied to the concentrations of copper ions released at the 1 mg/L mass loading rate to predict concentrations released at the higher mass loading rates of 10 and 100 mg/L, respectively.

The acute and chronic ecotoxicity of copper massive were evaluated by comparing the acute (7-day) and chronic (28-day) T/D values for copper massive from Rodriguez *et al.* (2012) and Rodriguez *et al.* (2017, as cited in ECI, 2018b) measured at a pH of 6 to the acute and chronic ERVs for copper, respectively, at pH 6 (see Table 4.6).

**Table 4.6 Comparison of Copper Transformation/Dissolution Values and Copper ERVs for Copper Massive Environmental Hazard Classifications**

Acute/Chronic	Copper Mass Loading Rate (mg/L)	Copper Massive T/D Value (µg copper/L)	Copper ERVs (µg copper/L)	GHS Classification
Acute	1	1.0	12	Acute Aquatic Toxicity Category 3
	10	10		
	100	100		
Chronic	1	3.4	13	Not Classified

Notes:

ERV = Ecotoxicity Reference Value; GHS = Globally Harmonized System of Classification and Labelling of Chemicals; T/D = Transformation/Dissolution.

All values are compared for a pH of 6.

ERVs are from ECI (2018b); T/D values are from Rodriguez *et al.* (2012) and Rodriguez *et al.* (2017, as cited in ECI, 2018b).

For acute aquatic toxicity, metals are classified into Category 1, 2, or 3 based on whether the release of copper ions from T/D testing exceeds the acute ERV at low (1 mg/L), medium (10 mg/L), and high (100 mg/L) mass loading rates, respectively (UN, 2017). Because copper massive's T/D value at 100 mg/L (100 µg/L) exceeds the acute copper ERV (12 mg/L), copper massive is classified as an Acute Aquatic Toxicity Category 3 hazard. An M factor is only applied for those substances classified as Category 1 acute aquatic toxicity hazards, so an M factor was not derived for the acute aquatic toxicity hazard classification for copper massive (UN, 2017). Notably, Acute Aquatic Toxicity Category 3 does not exist in the European Union's environmental hazard classification scheme (ECHA, 2017).

GHS hazard classification for chronic aquatic toxicity accounts for whether the metal of interest is considered rapidly removable from the water column and/or bioaccumulative. Copper massive is not classified as a chronic aquatic toxicity hazard because (1) copper metal is considered both rapidly removable and non-bioaccumulative, and (2) the measured concentration of copper ions released in 28-day T/D testing of copper massive at a mass loading rate of 1 mg/L and a pH of 6 (3.4 µg/L) is lower than the chronic copper ERV at pH 6 (13 µg/L) (see Table 4.6).

### 4.3 Copper Powder

The SSA used for determining environmental hazard classifications for copper powder was 67 mm<sup>2</sup>/mg, based on a spherical particle size of 10 µm (Rodriguez *et al.*, 2007, as cited in ECI, 2018b; Rodríguez *et al.*, 2011). This is a reasonable "worst-case" (*i.e.*, finest) SSA for copper powder. Table 4.7 provides the GHS environmental hazard classifications for copper powder and a summary of the justification for each classification.

**Table 4.7 Summary of GHS Environmental Hazard Classifications for Copper Powder and Justification**

Endpoint	GHS Classification	Justification
Acute Aquatic Toxicity	Category 1 (M factor = 1)	The release of copper ions in 7-day T/D testing of copper wire and copper massive (which have similar surface loading rates as copper powder) measured at a mass loading rate of 1 mg/L and a pH of 6 (27.5 µg/L) exceeds the acute copper ERV at pH 6 (12 µg/L). Therefore, copper powder is classified as an Acute Aquatic Toxicity Category 1 hazard. An M-factor of 1 is applied for copper powder because the copper powder L(E)C <sub>50</sub> ( <i>i.e.</i> , the acute copper ERV corrected for copper powder's solubility) at pH 6 is 0.436 mg/L, which is between 0.1 and 1 mg/L (UN, 2017).
Chronic Aquatic Toxicity	Category 3	Copper powder is classified as a Chronic Aquatic Toxicity Category 3 hazard, because the predicted concentration of copper ions released from 28-day T/D testing of copper powder at a mass loading rate of 1 mg/L and a pH of 6 (110 µg/L) is greater than the chronic copper ERV at pH 6 (13 µg/L), but the predicted copper ion release in 28-day T/D testing of this substance at a lower 0.1 mg/L mass loading rate and a pH of 6 (11 µg/L) is not.
Hazardous to the Ozone Layer	Not Classified	GHS hazard classification as a substance that is hazardous to the ozone layer requires that a substance either be listed in the Annexes of "The Montreal Protocol on Substances that Deplete the Ozone Layer" (UNEP, Ozone Secretariat, 2017) or contain a substance listed therein. Copper is not listed in the Annexes of the Montreal Protocol, and therefore copper powder is not classified as hazardous to the ozone layer under the GHS.

Notes:

ERV = Ecotoxicity Reference Value; T/D = Transformation/Dissolution.

ERVs from ECI (2018b); T/D values are from Rodriguez *et al.* (2007, as cited in ECI, 2018b) and Rodríguez *et al.* (2011).

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

Skeaff and Hardy (2005, as cited in ECI, 2018b) assessed the bioavailability of copper powder (SSA between 48 and 107 mm<sup>2</sup>/mg) in a 7-day T/D test. Tests were conducted with mass loading rates of 1 and 100 mg/L at a pH of 6. The measured release of copper ions from the test substance was 82 µg/L for the mass loading rate of 1 mg/L (coefficient of variation = 32%) and 1,118 µg/L for the mass loading rate of 100 mg/L (coefficient of variation = 34%). The authors noted that the high variability between the two mass loading rates may have been related to particle abrasion, which increases copper ion release into solution. Given the uncertainty about the SSA of the powder, the variability (high coefficients of variation), and the likely inter-particle abrasion, these results are not used directly for classification purposes, but are shown in order to support the WoE.

Instead, the more reliable results from Rodriguez *et al.* (2007, as cited in ECI, 2018b) and Rodríguez *et al.* (2011) were used for determining the environmental hazard classifications for copper powder, assuming an SSA of 67 mm<sup>2</sup>/mg (corresponding to a particle diameter of 10 µm). These two studies were conducted with samples of copper wire and copper massive embedded in epoxy resin (Rodríguez *et al.*, 2007, as cited in ECI, 2018b), but the surface loading concentrations used in these tests were within the predicted range of concentrations for copper powder. The authors assessed the T/D of copper massive in a 7-day test at a mass loading rate of 1 mg/L. See Table 4.8 for study results. The data collected at a pH of 6 were retained to determine the environmental hazard classifications for copper powder, because these data resulted in the highest concentration of copper ions released from the test substance. As previously noted, for assessing acute hazards, the SSA for the smallest particle size for copper powder (*i.e.*, 67 mm<sup>2</sup>/mg) was used to

convert the concentration of copper ions released per unit surface area ( $\mu\text{g}/\text{mm}^2$ ) to the concentration of copper ions released from the substance ( $\mu\text{g}/\text{L}$ ) at a mass loading rate of 1 mg/L.

**Table 4.8 Results from the Transformation/Dissolution Test for Copper Powder**

Transformation/Dissolution Test		Release of Copper Ions Per Unit Surface Area ( $\mu\text{g}/\text{mm}^2$ )			Release of Copper Ions from Copper Powder ( $\mu\text{g}$ copper/L)		
Mass Loading Rate (mg copper/L)	Time (Days)	pH 6	pH 7	pH 8	pH 6	pH 7	pH 8
1 mg/L	7 (acute)	0.41	0.19	0.13	27.5	12.7	8.7
1 mg/L <sup>1</sup>	28 (chronic)				<b>110</b>	<b>50.8</b>	<b>34.8</b>
0.1 mg/L <sup>2</sup>					<b>11</b>	<b>5.1</b>	<b>3.5</b>

Notes:

Highlighted values are those that were used to determine the environmental hazard classifications for copper powder.

Sources: Rodríguez *et al.* (2007, as cited in ECI, 2018b); Rodríguez *et al.* (2011).

(1) Bolded values were adjusted from those measured in the 7-day test to predict the results of a 28-day test by multiplying the 7-day test results by a factor of 4.

(2) Bolded values were adjusted from the predicted values for a mass loading rate of 1 mg/L to predict those for a mass loading rate of 0.1 mg/L by dividing the former by a factor of 10.

The acute and chronic ecotoxicity of copper powder were evaluated by comparing the acute (7-day) and chronic (28-day) T/D values for copper wire and copper massive from Rodríguez *et al.* (2007, as cited in ECI, 2018b) and Rodríguez *et al.* (2011) measured at a pH of 6 to the acute and chronic copper ERVs, respectively, at pH 6 (see Table 4.9).

**Table 4.9 Comparison of Copper Transformation/Dissolution Values and Copper ERVs for Copper Powder Environmental Hazard Classifications**

Acute/Chronic	Copper Mass Loading Rate (mg/L)	Copper Wire/Massive T/D Value ( $\mu\text{g}$ copper/L)	Copper ERVs ( $\mu\text{g}$ copper/L)	GHS Classification
Acute	1	27.5	12	Acute Aquatic Toxicity Category 1 (M factor = 1)
Chronic	1	110	13	Chronic Aquatic Toxicity Category 3
	0.1	11		

Notes:

ERV = Ecotoxicity Reference Value; GHS = Globally Harmonized System of Classification and Labelling of Chemicals; T/D = Transformation/Dissolution.

All values are compared for a pH of 6.

ERVs from are ECI (2018b); T/D values are from Rodríguez *et al.* (2007, as cited in ECI, 2018b) and Rodríguez *et al.* (2011).

For acute aquatic toxicity, metals are classified into Category 1, 2, or 3 based on whether the release of ions from T/D testing exceeds the acute ERV at low (1 mg/L), medium (10 mg/L), and high (100 mg/L) mass loading rates, respectively (UN, 2017). The release of copper ions in 7-day T/D testing of copper substances with similar surface loading rates as copper powder (27.5  $\mu\text{g}/\text{L}$ ) exceeds the acute copper ERV (12  $\mu\text{g}/\text{L}$ ) at the low mass loading rate of 1 mg/L. For this reason, it was unnecessary to extrapolate from the author's results to predict T/D values at higher mass loading rates (as was done for copper massive). Therefore, copper powder is classified as an Acute Aquatic Toxicity Category 1 hazard. An M-factor of 1 is applied for copper powder because the copper powder L(E)C<sub>50</sub> (*i.e.*, the acute copper ERV corrected for copper powder's solubility) at pH 6 is 0.436 mg/L, which is between 0.1 and 1 mg/L (UN, 2017).

GHS hazard classification for chronic aquatic toxicity accounts for whether the metal of interest is considered rapidly removable from the water column and/or bioaccumulative. Copper powder is classified as a Chronic Aquatic Toxicity Category 3 hazard because the predicted concentration of copper ions released in 28-day T/D testing of copper powder at 1 mg/L and a pH of 6 (110 µg/L) is greater than the chronic copper ERV of pH 6 (13 µg/L), but the predicted concentration of copper ions released in 28-day T/D testing of this substance at a lower 0.1 mg/L mass loading rate and a pH of 6 (11 µg/L) is not (see Table 4.9). This hazard classification approach is consistent with the logic behind the guidance provided in Table 4.1.1(b)(ii) of the 7<sup>th</sup> Revised Edition of the GHS (UN, 2017) and with ECHA's "Guidance on the Application of the CLP Criteria" (ECHA, 2017). An M factor is only applied for those substances classified as Category 1 chronic aquatic toxicity hazards, so an M factor was not derived for the chronic aquatic toxicity hazard classification for copper powder (UN, 2017).

#### 4.4 Coated Copper Flakes

The particle size of coated copper flakes ranges from 5-100 µm (ECI, 2008). Assuming spherical particles, an equivalent SSA would range from 6.5-135 mm<sup>2</sup>/mg. Coated copper flakes are characterized as fine flakes coated with aliphatic acids, which prevents aggregation, thus increasing the flakes' surface area. Therefore, the actual SSA for coated copper flakes is extremely high, ranging from 2,080-2,900 mm<sup>2</sup>/mg – this range of values was used for determining the environmental hazard classifications for coated copper flakes. Table 4.10 provides the GHS environmental hazard classifications for coated copper flakes and a summary of the justification for each classification.

**Table 4.10 Summary of GHS Environmental Hazard Classifications for Coated Copper Flakes and Justification**

Endpoint	GHS Classification	Justification
Acute Aquatic Toxicity	Category 1 (M factor = 10)	The release of copper ions from 7-day T/D testing of coated copper flakes (721 µg/L) at a mass loading rate of 1 mg/L and a pH of 6 exceeds the acute copper ERV at pH 6 (12 µg/L). Therefore, coated copper flakes are classified as Acute Aquatic Toxicity Category 1 hazard. An M factor of 10 is applied for coated copper flakes because the L(E)C <sub>50</sub> value for coated copper flakes ( <i>i.e.</i> , the acute copper ERV corrected for coated copper flakes' solubility) is 0.017 mg/L, which is between 0.01 and 0.1 mg/L (UN, 2017).
Chronic Aquatic Toxicity	Category 2	Coated copper flakes are classified as Chronic Aquatic Toxicity Category 2 hazard, because the concentration of copper ions released from 28-day T/D testing of coated copper flakes at a mass loading rate of 0.1 mg/L and a pH of 6 (77.3 µg/L) is greater than the chronic copper ERV at pH 6 (13 µg copper/L), but the predicted release of copper ions in 28-day T/D testing of this substance a mass loading rate of 0.01 and a pH of 6 (7.7 µg/L) is not.
Hazardous to the Ozone Layer	Not Classified	GHS hazard classification as a substance that is hazardous to the ozone layer requires that a substance either be listed in the Annexes of "The Montreal Protocol on Substances that Deplete the Ozone Layer" (UNEP, Ozone Secretariat, 2017) or contain a substance listed therein. Copper is not listed in the Annexes of the Montreal Protocol, and therefore coated copper flakes are not classified as hazardous to the ozone layer under the GHS.

Notes:

ERV = Ecotoxicity Reference Value; T/D = Transformation/Dissolution.

ERVs from ECI (2018b); T/D values from Schaefers and Klawonn (2013, as cited in ECHA, 2014b).

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017).

To determine the bioavailability and toxicity of coated copper flakes in the aquatic environment, an OECD Test Guideline 29 T/D study was performed with coated copper flakes (mean diameter: 9-11 µm) at pH 6 and pH 7, with measurements taken at 7 and 28 days (Schaefers and Klawonn, 2013, as cited in both ECHA, 2014b and ECI, 2014). The data from this study demonstrate higher copper ion releases at acidic conditions (pH 6) compared to neutral conditions (pH 7). Further, at a mass loading rate of 1 mg/L coated copper flakes under acidic conditions (pH 6), the dissolved mean copper concentration (acute) (721 µg/L) is comparable to the dissolved mean copper equilibrium concentration (chronic) (773 µg/L). However, at a mass loading rate of 1 mg/L coated copper flakes at pH 7, there is a two-fold difference between the dissolved mean copper concentration (acute) and dissolved mean copper equilibrium concentration (chronic). Thus, retaining the data collected at a pH of 6 to determine the environmental hazard classifications for coated copper flakes was deemed to be conservative, because these data resulted in the highest concentration of copper ions released from the test substance (see Table 4.11).

**Table 4.11 Results from the Transformation/Dissolution Test for Coated Copper Flakes**

Transformation/Dissolution Test		Mean Copper Ion Concentration Released from Coated Copper Flakes (µg dissolved copper/L) <sup>1</sup>	
Mass Loading Rate (mg copper/L)	Time (Days)	pH 6	pH 7
1 mg/L	7 (acute)	721	363
1 mg/L	28 (chronic)	773	639
0.1 mg/L <sup>2</sup>		<b>77.3</b>	<b>63.9</b>
0.01 mg/L <sup>2</sup>		<b>7.7</b>	<b>6.4</b>

Notes:

T/D = Transformation/Dissolution.

Highlighted values are those that were used to determine the environmental hazard classifications for coated copper flakes.

Source: Schaefers and Klawonn (2013, as cited in ECHA, 2014b).

(1) T/D tests were not conducted at pH 8 for coated copper flakes (ECI, 2014).

(2) Bolded values were extrapolated from the mean copper ion concentration released at the 1 mg/L mass loading rate to predict mean concentrations released at lower mass loading rates of 0.1 and 0.01 mg/L by dividing the former by 10 and 100, respectively.

The acute and chronic ecotoxicity of coated copper flakes were evaluated by comparing the acute (7-day) and chronic (28-day) T/D values for coated copper flakes from Schaefers and Klawonn (2013, as cited in both ECHA, 2014b and ECI, 2014) measured at a pH of 6 to the acute and chronic copper ERVs, respectively, at pH 6 (see Table 4.12).

**Table 4.12 Comparison of Copper Transformation/Dissolution Values and Copper ERVs for Coated Copper Flakes Environmental Hazard Classifications**

Acute/Chronic	Copper Mass Loading Rate (mg/L)	Coated Copper Flakes T/D Values (µg copper/L)	Copper ERVs (µg copper/L)	GHS Classification
Acute	1	721	12	Acute Aquatic Toxicity Category 1 (M factor = 10)
Chronic	1	773	13	Chronic Aquatic Toxicity Category 2
	0.1	77.3		
	0.01	7.7		

Notes:

ERV = Ecotoxicity Reference Value; GHS = Globally Harmonized System of Classification and Labelling of Chemicals; T/D = Transformation/Dissolution.

All values are compared for a pH of 6.

ERVs are from ECI (2018b); T/D values are from Schaefers and Klawonn (2013, as cited in ECHA, 2014b).

For acute aquatic toxicity, metals are classified into Category 1, 2, or 3 based on whether the release of ions from T/D testing exceeds the acute ERV at low (1 mg/L), medium (10 mg/L), and high (100 mg/L) mass loading rates, respectively (UN, 2017). The release of copper ions in 7-day T/D testing of coated copper flakes (721 µg/L) exceeds the acute copper ERV (12 µg/L) at the low mass loading rate of 1 mg/L (see Table 4.12). Therefore, coated copper flakes are classified as an Acute Aquatic Toxicity Category 1 hazard. An M factor of 10 is applied for coated copper flakes because the L(E)C<sub>50</sub> value for coated copper flakes (*i.e.*, the acute copper ERV corrected for coated copper flakes' solubility) at pH 6 is 0.017 mg/L, which is between 0.01 and 0.1 mg/L (UN, 2017).

GHS hazard classification for chronic aquatic toxicity accounts for whether the metal of interest is considered rapidly removable from the water column and/or bioaccumulative. Coated copper flakes are classified as a Chronic Aquatic Toxicity Category 2 hazard, because the concentration of copper ions released in 28-day T/D testing of coated copper flakes measured at a lower mass loading rate of 0.1 mg/L and a pH of 6 (77.3 µg/L) is greater than the chronic copper ERV at pH 6 (13 µg/L), but the predicted release of copper ions in 28-day T/D testing of this substance at a loading rate of 0.01 and a pH of 6 (7.7 µg/L) is not (see Table 4.12). An M factor is only applied for those substances classified as Category 1 aquatic toxicity hazards, so an M factor was not derived for the chronic aquatic toxicity hazard classification for coated copper flakes (UN, 2017).

Although the GHS hazard classification for chronic aquatic toxicity for coated copper flakes, which is based on the most relevant currently available data presented above, is Category 2, it is important to note that coated copper flakes are assigned a mandatory Category 1 hazard (M factor = 1) under the CLP hazard classification scheme in the European Union (under EC No. 1272/2008; EC, 2016). The CLP classification for chronic aquatic toxicity used a surrogate approach, because the chronic toxicity data for coated copper flakes were considered inadequate at the time (ECHA, 2014a). In addition, the assessment of coated copper flakes did not consider copper to be rapidly removable from the water column (ECHA, 2014a).

## 4.5 Summary of Environmental GHS Hazard Classifications

The following environmental hazard classifications are based on the principals and classification criteria presented in the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017). Copper massive is classified as an Acute Aquatic Toxicity Category 3 hazard. Copper powder is classified as an Acute Aquatic Toxicity Category 1 (M factor = 1) and Chronic Aquatic Toxicity Category 3 hazard. Finally, coated copper flakes are classified as an Acute Aquatic Toxicity Category 1 (M factor = 10) and Chronic Aquatic Toxicity Category 2 hazard. Table 4.13 summarizes these hazard classifications and presents the GHS hazard statement codes, when applicable.

**Table 4.13 Summary of GHS Environmental Hazard Classifications for Copper Metal Forms**

Copper Metal Form	GHS Hazard Classifications	GHS Hazard Statement Code
Copper Massive  CAS: 7440-50-8 EC: 231-159-6	Acute Aquatic Toxicity Category 3	H402: Harmful to aquatic life
Copper Powder  CAS: 7440-50-8 EC: 231-159-6	Acute Aquatic Toxicity Category 1 (M factor = 1)	H400: Very toxic to aquatic life
	Chronic Aquatic Toxicity Category 3	H412: Harmful to aquatic life with long lasting effects
Coated Copper Flakes  No CAS or EC numbers allocated	Acute Aquatic Toxicity Category 1 (M factor = 10)	H400: Very toxic to aquatic life
	Chronic Aquatic Toxicity Category 2	H411: Toxic to aquatic life with long lasting effects

Notes:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017); M Factor = Multiplying Factor.

## 5 Discussion

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The GHS hazard classifications for each form of copper metal evaluated herein (copper massive, copper powder, and coated copper flakes) are presented in Table 5.1 and summarized below. These hazard classifications are based on the 7<sup>th</sup> Revised Edition of the GHS guidance (UN, 2017) and were derived using a WoE approach, using read-across data when appropriate.

- Based on the available data, no human health hazard classifications are required for copper massive or copper powder. Hazard classification for this copper metal form was based on a WoE approach, using data on surrogate copper compounds when necessary and considering the bioavailability and solubility of these two copper metal forms.
- Coated copper flakes are unique both chemically and toxicologically from the other forms of copper metal evaluated herein, and this is reflected in the human health hazard classifications for this substance. Toxicological data for coated copper flakes are available for most human health hazard endpoints. Coated copper flakes are classified as an Acute Oral Toxicity Category 4, Acute Inhalation Toxicity Category 3, and Eye Irritation Category 2A hazard.
- In the context of aquatic environment hazard classification, all three forms of copper metal were considered both rapidly removable from the water column and non-bioaccumulative.
- The GHS criteria for classifying copper metal compares the inherent toxicity of copper ions (in the form of ERVs) to the amount and rate of copper ions released from each form of copper metal (determined by T/D tests).
- Due to its large particle size and small surface area, copper massive is less hazardous to the aquatic environment compared to copper powder and coated copper flakes. Copper massive is classified as an Acute Aquatic Toxicity Category 3 hazard. Notably, this acute aquatic toxicity hazard category does not exist in the European Union's hazard classification scheme (ECHA, 2017).
- Copper powder is classified as an Acute Aquatic Toxicity Category 1 hazard (and an M factor of 1) and as a Chronic Aquatic Toxicity Category 3 hazard. Coated copper flakes are classified as an Acute Aquatic Toxicity Category 1 hazard (and an M factor of 10) and a Chronic Aquatic Toxicity Category 2 hazard.



**Table 5.1 Summary of GHS Hazard Classifications for Copper Metal**

<b>Copper Metal Form</b>	<b>GHS Hazard Classifications</b>
Copper Massive CAS: 7440-50-8, EC: 231-159-6	Acute Aquatic Toxicity Category 3
Copper Powder CAS: 7440-50-8, EC: 231-159-6	Acute Aquatic Toxicity Category 1 (M factor = 1) Chronic Aquatic Toxicity Category 3
Coated Copper Flakes No CAS or EC numbers allocated	Acute Oral Toxicity Category 4 Acute Inhalation Toxicity Category 3 Eye Irritation Category 2A Acute Aquatic Toxicity Category 1 (M factor = 10) Chronic Aquatic Toxicity Category 2

Notes:

GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2017); M Factor = Multiplying Factor.

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