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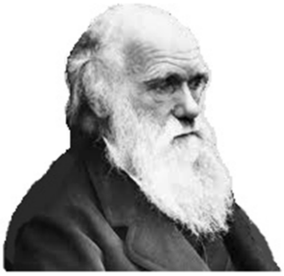

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Phytoplankton Susceptibility Towards Toxic Heavy Metal Cadmium: Mechanism and Its Recent Updates

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ABSTRACT

Environmental pollution particularly heavy metal pollution into aquatic ecosystem has led to multiple damage in almost all life forms. Cadmium is one of the priority pollutant listed by United States Environmental Protection Agency or US EPA that widely known to have an adverse effect to organisms as well as human health. One type of organism that is susceptible to the effects of metal pollution is phytoplankton. Phytoplankton is a group of microalgae that are easy to find and are primary producers in aquatic environments. Phytoplankton plays an important role in aquatic ecosystems because they serve as primary producers. They are representing the water total primary productivity and reinforcing the aquatic life on the higher food chain. Thus, any threats that endangered the population of phytoplankton can lead to trophical cascade or even worse, biodiversity loss. The exposure of cadmium in high concentration to phytoplankton can lead to various impact including cell damage and disruption, biosynthesis inhibition of photosynthetic pigment (e.g. chlorophyll and carotenoid), chlorphyll degradation or known as chlorosis, thylakoid membrane degradation, inhibition of cellular metabolism and cell division. It is important to study the impact of cadmium to phytoplankton in a cellular level to better understand what mechanism lies and to what extent that the cadmium will be transferred to higher trophical organism via bioaccumulation or biomagnification.

Keywords**:** Cadmium, Heavy Metals, Phytoplankton, Toxicity

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1. INTRODUCTION

Growing activities of human civilization for more than centuries has led to significant advances in many sectors, including industrial, agriculture, and health. The creation and production of chemicals that support those strategic sectors has also been reported to be exponentially increase throughout the year, reaching thousands to millions in number per 2020 and projected to be doubled by the end of 2024 [1]. This growing event accompanied by the intensify concern from scientist regarding its fate and environmental safety. To date, of all approximately millions chemicals, only few has been studied thoroughly [2]. The information about each of these synthetically produced chemicals is critically needed to evaluate its safety thus we can reduce its possibly-generated environmental consequences.

One type of chemicals that caused environmental pollution is heavy metals. Heavy metals are widely used in industrial activities, such as batteries, fuels, and mining [3]. The process of removing heavy metals that are not managed properly can have a negative impact on other activities, such as agricultural activities. Several types of heavy metals that pollute the environment are zinc (Zn), mercury (Hg), and cadmium (Cd) [4]. Cadmium (Cd) is a silver-white heavy metal [5]. Cadmium is naturally found in soil, water and the earth's crust [6]. Cadmium concentrations in nature can increase due to natural disasters and human activities (anthropogenic) such as zinc (Zn) mining [7].

Excess cadmium concentration in the environment can lead to multiple physiological adversity. In plants, cadmium can affect nutrient uptake [8] and reduce the number of chloroplasts [9]. In humans, cadmium toxicity can cause impaired kidney function that causes symptoms of glycosuria [10]. In aquatic environments, concentrated cadmium will possibly enter the body of biota through a bioaccumulation process by passing through the skin, respiratory tract and digestive tract. This bioaccumulation can occur through the food chain in aquatic living organisms which can lead to food for humans and endanger health. For aquatic organisms, cadmium can affect the growth, reproduction and development of an organism.

One type of organism that is susceptible to the effects of metal pollution is phytoplankton. Phytoplankton is a group of microalgae that are easy to find and are primary producers in aquatic environments [11]. Phytoplankton plays an important role in aquatic ecosystems because they serve as primary producers. They are representing the water total primary productivity and reinforcing the aquatic life on the higher food chain. Thus, any threats that endangered the population of phytoplankton can lead to trophical cascade or even worse, biodiversity loss. Microalgae are also known to be very sensitive to heavy metals so they are often used as indicators of heavy metals [11] .

Phytoplankton are generally not selective in choosing the chemical elements to be absorbed. This causes cadmium can also be absorbed by any species of phytoplankton. Cadmium exposure to algae can have a negative effect on the growth of *phytoplankton* [12]. This is influenced by the length of exposure time and the amount of cadmium concentration [13]. Cadmium can enter algal cells through metal transporters and can damage photosystems [14]. Therefore, cadmium exposure can cause chlorophyll damage and thylakoid membrane degradation according to Purbonegoro [15] and inhibit cellular division in algae [12].

The potential for environmental pollution by cadmium is quite large. Data from the United States Geological Survey shows the value of cadmium production in 2014 reached 22,700 metric tons. According to the Agency for Toxic Substances and Disease Registry and the International Agency of Research on Cancer, cadmium is a priority compound number 7 out of 20 and ranks first as a carcinogenic element. In Indonesia, cadmium is reported to be one of the main pollutants in agricultural land in the Pantura area, West Java. It was reported that cadmium with levels reaching 8.75 ppm had polluted agricultural land covering an area of 106 thousand hectares in Karawang and Bekasi, West Java. The concentration of cadmium exceeds the threshold of the Regulation of the Minister of the Environment Number 51 of 2004, which is 0.01 g/l. This review study will examine the state of the art of cadmium and its fate in environment along its toxicity. A mechanistic toxicity study towards phytoplankton species as well as its recently reported concentration threshold will also be discussed thoroughly.

2. CADMIUM

Metals are substances with high electrical conductivity which will lose electrons to form cations [16]. Metals are found naturally in the earth's crust and their composition varies between different locations, resulting in spatial variations in concentrations around them. The distribution of metals in the atmosphere is monitored by the properties of the given metal and by various environmental factors [17]. The most common heavy metals found in wastewater include arsenic, cadmium, chromium, copper, lead, nickel, and zinc, all of which pose risks to human health and the environment [18]. Heavy metals enter the environment naturally and through human activities. Various sources of heavy metals include soil erosion, natural weathering of the earth's crust, mining, industrial waste, urban runoff, sewage disposal, insect or disease control agents applied to plants, and many others [16].

Cadmium (Cd) is a heavy metal which has a molecular weight of 112.4 grams/mol. Cadmium is solid and silver in color. Cadmium has a boiling point of 765 °C (1409 F) and a melting point of 320.9 °C (609.6 F) [19]. Cadmium is a relatively rare metal but is often used for various purposes. In its pure state, cadmium is silver in color with a hint of blue. Metal is very soft and can be easily cut with a knife [20]. Pure cadmium cannot be found in nature. How to get pure cadmium only by combining it with the components of other elements. These components are substances that are formed when two or more elements are combined in a chemical reaction. Cadmium can only be purified by humans. This metal has no odor and taste but is very toxic [20]. The main sources of cadmium from human activities are mining, metallurgical industry and sewage sludge. In mining activities, cadmium is usually found in mineral ores including sulfide *green ockite* (*xanthochroite*), otative carbonate, and cadmium oxide. These minerals are formed in association with sphalerite ores and their oxides, or obtained from dust left over from electrolytic sludge processing [5].

The average annual production of cadmium throughout the world increased from only 20 tonnes in the 1920s to about 12 000 tonnes in the period 1960–1969, 17 000 tonnes in 1970–1984; since 1987 it has fluctuated around 20 000 tonnes [21]. A very large amount of Cd about 25,000 tons a year is released into the environment naturally. In the European Union and worldwide, approximately 85–90% of total airborne cadmium emissions arise from anthropogenic sources, mainly from smelting and refining of nonferrous metals, fossil fuel combustion and municipal waste incineration. The natural source of cadmium is volcanic emissions. The total atmospheric emission of cadmium in western Europe was estimated at 1144 tonnes/year in 1982. It is estimated that with the application of the best available technology to control emissions in nonferrous smelters this amount can be cut by 34% in the 1990s. In European Union Member States, atmospheric emissions of cadmium in 1990 amounted to 158 tonnes/year distributed as follows: natural, 9.3%; nonferrous metal industry, 20.4%; oil combustion, 17.9%; waste incineration, 17.5%; iron and steel industry, 15.3%; coal combustion, 13.4%; cement manufacture, 4.4%; and others, 1.8% [22].

The disposal of industrial waste results in cadmium originating from the mainland having the largest role in increasing the concentration of heavy metals in the waters. During the rainy season, cadmium found on land is carried to the sea through rivers. Cadmium found in water exists in various forms such as dissolved, precipitated, or fine granules. Cadmium dissolved in waters will eventually settle but it takes quite a long time [16]. The solubility of cadmium in water is strongly influenced by its acidity, cadmium that is bound or precipitated can dissolve when there is an increase in acidity.

If the amount of cadmium that enters the cells of an organism is very large, then these cells cannot neutralize cadmium and can cause inhibition of the rate of growth and development, abnormalities in cell shape or cell organelles and damage the function of cell organelles. Cadmium contained in diatoms can affect metabolic processes, such as disturbances in photosynthetic pigments so that the growth of diatoms is inhibited [23].

Based on research by [24], the concentration of cadmium in Kamal Muara waters is 0.006 mg/L in water and 0.439 mg/L in sediments. While another reported [25] research on Jakarta Bay and the cadmium content contained in the range between 0.08-0.42 mg/L in water and 0.001-0.44 in sediment. According to Government Regulation 82 of 2001, the quality standard for cadmium in waters is 0.01 mg/L. Referring to the regulation, the cadmium content in the waters of Kamal Muara is still relatively low in water but quite high in sediments, while the concentration of cadmium in waters in Jakarta Bay is quite high in water and sediment.

If the cadmium pollution is compared to several other areas outside the province of Jakarta, there are several areas that have higher cadmium content than the waters in Jakarta, such as 0.0091 mg/L in the Musi River [26], 0.015 mgL in Kwanyar [27] and 0.0093 mg/L in the Pangkajene River [28]. However, there are also some areas that have cadmium content which is almost equivalent to the waters in Jakarta, such as the Citarum River [29] and the Bayuasin River [30] which have cadmium content of 0.003-0.01 mg/L and 0.002 -0.062 mg/L. While in Socah waters the cadmium content is very low with a value of 0-0.0001 [27] which indicates that there are still waters that are not too polluted in Indonesian waters. Several other studies regarding the content of cadmium in waters in Indonesia can be seen in Table 1.

Table 1. Cadmium Occurance in Water Bodies in Indonesia.

Location	Cadmium Concentration (mg/L)	Reference
Jakarta Bay	0.08-0.42	[25]
Kamal Estuary, Jakarta	0.006	[24]
Musi River, Palembang	0.0091	[26]
Socah, Bangkalan	0-0.0001	[27]
Kwanyar, Bangkalan	0.015-0.018	[27]
Citarum River, West Java	0.003-0.01	[29]

Banyuasin River, South Sumatra	0.002-0.062	[30]
Pangkajene River, South Sulawesi	0.0093	[28]
Coastal waters at Pelabuhan Ratu	< 0.001	[31]
Digul River Estuary and Arafura Sea	0.001 – 0.002	
Jakarta Bay	< 0.001	
Coastal Waters of Banten Province	< 0.001 – 0.001	
Jakarta Bay	< 0.001	
Cirebon Coastal Waters	0.001 – 0.002	
Kampar River, Riau	0.035 – 0.046	
East Kalimantan Waters (Sediment)	0.02 – 0.12*	
Watershed, Indragiri Regency, Riau	0.10-0.17	[32]
Bandung, West Java, Indonesia	0.86-9.69	
Pangalengan, West Java	0.18-4.06	
Cilacap. Central Java	0.01-0.54	
Brebes, Tegal, Central Java	1.83	
Bengawan River, Solo	0.08-0.13	
Wonokrono River, East Java	0.001-0.003	
Badung Regency, Bali	0.008-0.22	
North Pontianak, Kalimantan West	0.009-0.601	
Pantura, West Java	8.75	
South Sulawesi	0.005-0.015	

Cadmium that enters the human body can cause several disorders, namely digestive disorders such as diarrhea, abdominal pain and vomiting, reproductive organ disorders that cause reproductive failure and possibly even infertility, damage to several systems in the body such as the central nervous system and immune system, to DNA damage or cancer if it is chronic. Cadmium that enters the human body can come from various sources, which are mainly the environment and food. Food from the sea has the potential to contain more cadmium and other heavy metals because all industrial waste disposal into the waters will lead to the sea so that marine life consumed by humans is already exposed to a lot of heavy metals [19].

2. 1. Toxic Mechanism

The most dangerous and toxic form of cadmium is in the ionic form. This form is also naturally available [33]. If cadmium forms complex compounds with other ions, the toxicity of cadmium will decrease because the total concentration of Cd^{2+} is reduced in these compounds. Cadmium uptake in aquatic organisms is also known to decrease with increasing water hardness and alkalinity. In waters with high salinity, cadmium can be found in the form of $Cd_3(PO_4)_2$ [33].

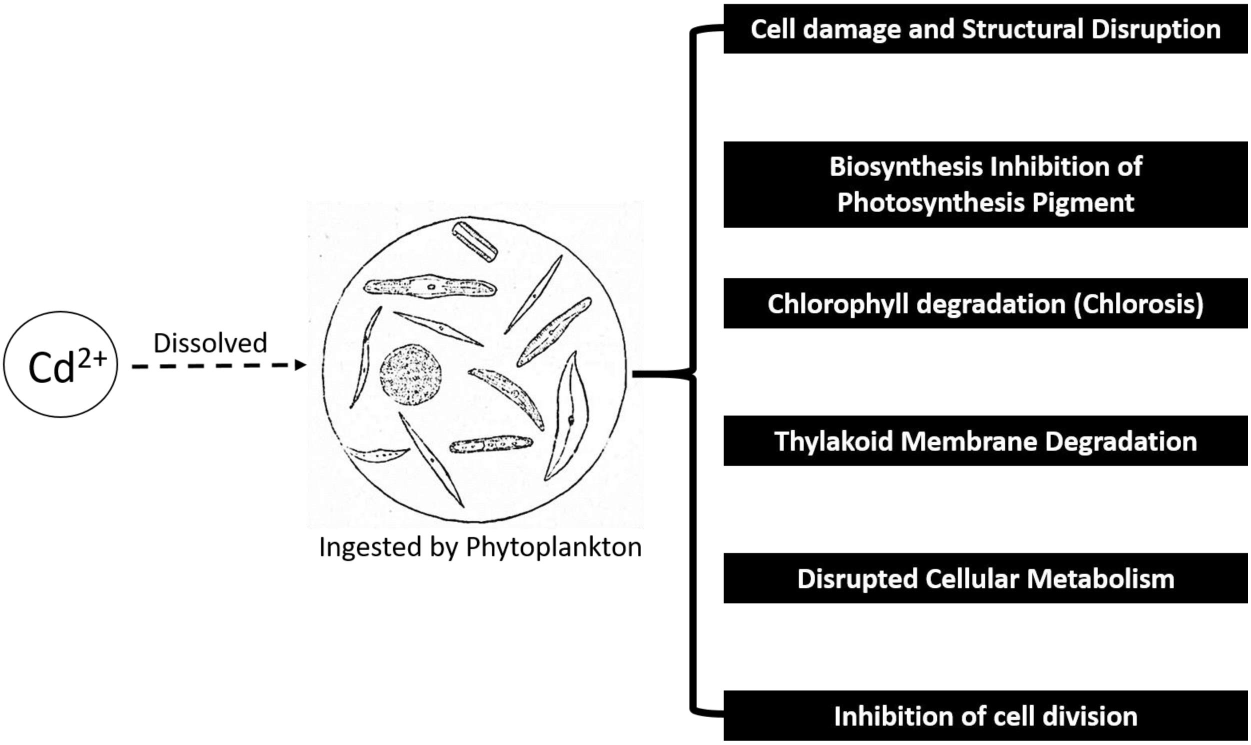

Figure 1. Schematic Cadmium Toxic Mechanism to Phytoplankton.

The mechanism of cadmium toxicity is not clearly understood but its effects on cells are known [34]. The concentration of cadmium increases 3,000-fold when it binds to cysteine-rich proteins such as metallothionein. In the liver, the cysteine-metallothionein complex causes hepatotoxicity and then circulates to the kidneys and accumulates in the kidney tissue causing nephrotoxicity. Cadmium has the ability to bind with cysteine, glutamate, histidine and aspartate ligands and can cause iron deficiency [35]. Cadmium and zinc have the same oxidation state and therefore cadmium can replace the zinc present in metallothionein, thereby inhibiting it from acting as a free radical scavenger in cells.

Cadmium is a heavy metal that is lipophilic, that is, it is soluble in lipids. This lipophilic nature allows cadmium to bind to cell proteins. This causes cadmium to be absorbed into phytoplankton cells with the help of enzymes such as permease enzymes and energy derived from ATP [15]. In addition, cadmium can enter cells with the help of *metal transporters* (ie, Ca and Fe transporters) which then inactivate the reaction center of PSII. This reaction center contains areas that carry chlorophyll for light gathering as well as carotenoids that function to protect algae from excess light [14].

This can cause algae to absorb cadmium in the surrounding aquatic environment until the amount contained in it far exceeds the concentration of cadmium in the surrounding water [36]. From algae, cadmium will accumulate in upper-level organisms through the food chain. However, this accumulation of cadmium in general will not lead to biomagnification [36].

3. IMPACT TO PHYTOPLANKTON

The absorption of heavy metals in phytoplankton occurs in two stages, namely [15]: 1) The initial stage consists of fast passive absorption and 2) followed by slow active absorption. At the cellular level, passive absorption is initiated by the interaction of heavy metals and cell walls. Cell walls contain extracellular enzymes that function in the absorption of elements needed by cells. In active absorption, heavy metals are transported through the cell membrane to the cytoplasm.

Growth in algae can be inhibited by high concentrations of cadmium compared to low concentrations of cadmium. It can also be influenced by the length of time cadmium exposure to algae [13]. In addition, excessive concentrations of cadmium can affect chloroplasts where there will be an increase in the activity of the galactolipase enzyme which triggers the hydrolysis of monogalactolipid molecules and causes degradation of the thylakoid membrane [15].

A compound can enter the cell membrane if the compound is lipophilic (easy to dissolve in fat or lipids). This is because the cell membrane is formed by two layers of lipids (*lipid bilayer*). Lipophilic compounds will dissolve in the lipid layer so that they can bind to cell proteins. The cell membrane is semipermeable to several ions such as sodium (Na^+) and potassium (K^+) as well as some heavy metals such as cadmium (Cd), copper (Cu), and zinc (Zn). In order to cross the cell membrane, a process of facilitated diffusion of heavy metal ions occurs. In the diffusion process, heavy metal ions are facilitated by permease enzymes which are cell membrane proteins that can bind to heavy metals so that they can pass through lipid membranes [15].

When heavy metal ions are already in the cell membrane, enzymes and cell organelles in the cytoplasm become the main destination for these ions. The organelles most sensitive to heavy metals are chloroplasts. Chloroplasts are organelles that act as sites in the photosynthesis process, which function to receive water and carbon dioxide and are converted into carbohydrates and oxygen with the help of sunlight [37]. Heavy metal ions that enter the chloroplast will affect the thylakoid membrane which is part of the chloroplast which functions to absorb sunlight. Cadmium will increase the activity of the enzyme galactolipase. The excessive increase in these enzymes triggers the hydrolysis of monogalactolipid molecules that make up the thylakoid membrane, thereby causing the degradation of the thylakoid membrane [38].

In general, cadmium will inhibit the biosynthesis of photosynthetic pigments in chloroplasts, namely chlorophyll and carotenoids [39]. Chloroplasts exposed to heavy metals can be damaged so that the photosynthesis process is disrupted. Chloroplasts cannot receive sunlight properly so they cannot convert water and carbon dioxide. If the photosynthesis process is disrupted, the phytoplankton cannot receive food and the oxygen levels produced are reduced.

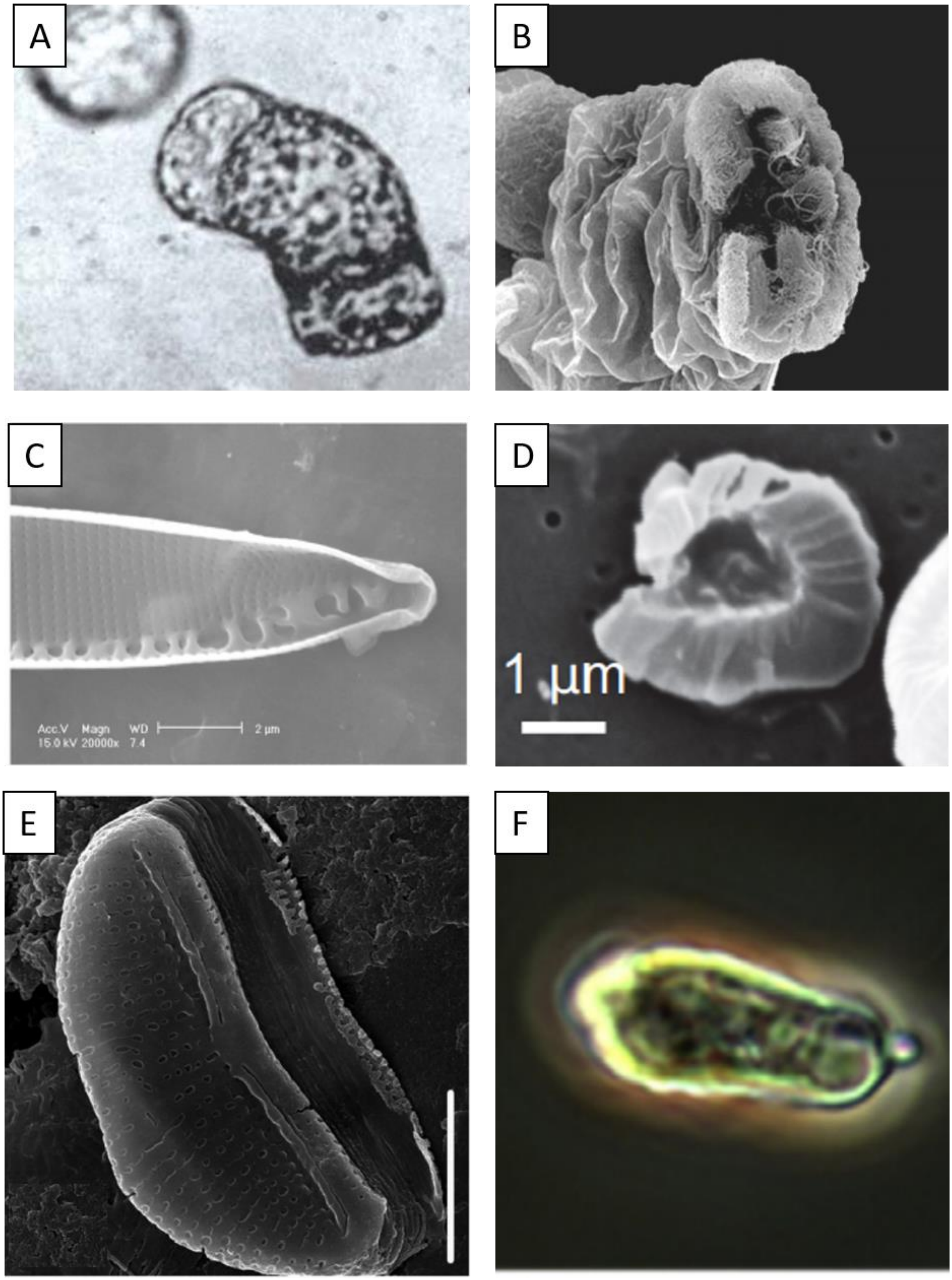

Figure 2. Phytoplankton Cell's Damage due to Cadmium Exposure in various species. *Thalassiosira aestivalis* (A), *Brachionus plicatilis* (B), *Nitzschia palea* (C), *Emiliania huxleyi (D), Halamphora veneta* (E), *Cryothecomonas armigera* (F) [42-47].

The decrease in the concentration of chlorophyll-*a* by cadmium can occur due to chlorosis. Chlorosis is a chlorophyll degradation process that is influenced by extreme conditions outside the cell. This chlorosis can occur through two pathways, namely, direct inhibition of the 5-aminolevulinic acid dehydratase enzyme which has a role in chlorophyll synthesis, and through the substitution of iron (Fe) and magnesium (Mg) metals involved in chlorophyll synthesis [15]. The inhibition of these enzymes causes the synthesis of chlorophyll not to occur optimally and the amount of chlorophyll production decreases [15]. Carotenoid synthesis can also be inhibited in the presence of heavy metal ions such as cadmium. The presence of these ions will generally trigger the production of carotenoids, but exposure to large amounts of heavy metals will reduce the carotenoid content [40].

According to research by Carfagna [41], cadmium can reduce photosynthetic activity in microalgae as much as 77% after entering the cell. Cadmium can enter cells by means of *metal transporters* (ie, Ca and Fe transporters) and is a dependent metabolic process. These heavy metals will then inactivate several reaction centers of PSII, which contain *internal antenna-domains* that carry chlorophyll for light gathering as well as carotenoids and *xanthophylls* that function to protect algae from excess light [14].

In addition, ionized cadmium (Cd^{2+}) can attack and inhibit the photosynthesis process, namely by degrading the thylakoid membrane. This degradation causes inhibition of chemical reactions in photosynthesis and can reduce chlorophyll levels. The effect of this is seen in the inhibition of ATP and NADPH production during the photosynthesis process. With decreased production of ATP and NADPH, some activities of microalgae will be inhibited, such as respiration and cellular metabolism. In addition to stunted growth, disruption of this metabolic process can also cause cell death [48].

When cadmium has entered the cell membrane, many cell organelles in the cytoplasm will be affected by cadmium such as mitochondria, vacuoles, ribosomes, chloroplasts, and other organelles. The concentration of cadmium that enters the cytoplasm will be localized into some of these cell organelles so that large concentrations are needed to affect chloroplasts which have an impact on chlorophyll levels [49].

Inhibition on growth of *Thalassiosira* sp. caused by cadmium which causes morphological changes in cells and inhibits cell division. In addition, cadmium can attack protein synthesis and cell organelles such as mitochondria [40]. According to Kaur & Bhatnagar [50], the toxic effect of cadmium causes *Thalassiosira fluviatilis* and *Thalassiosira aestivalis to* lose the ability to absorb nutrients such as nitrates and disrupt cell metabolism by stimulating cell elongation. Cadmium is also known to enter cells and exchange important heavy metal ions in enzymes. This enzyme will then damage the metabolic process by blocking and decreasing the thiol group in the protein, which functions for the formation of antioxidant enzymes such as glutathione and metallothionein. The presence of metal ions is very important to block oxygen reduction reactions in cells and in detoxification of heavy metals [50].

At high concentrations of cadmium, cell wall morphology can change and seta disappear. In addition, high concentrations cause reduced chlorophyll production so that the color of chlorophyll cannot be seen clearly on a microscope. Cell wall morphological changes can occur due to the bioabsorption process of cadmium in the diatom cell wall. The cell wall is the first cell barrier in the absorption of heavy metals so it is a defensive mechanism that makes diatoms tolerate metals in their medium. Cadmium that enters through the cell wall will damage the formation of the cell wall so that its shape becomes more round and not rectangular [51].

Various species of microalgae have been studied to have a high level of sensitivity to metal cadmium. Below are data from several studies on the effect of cadmium on microalgae and diatom species. The data displayed is the ICvalue$_{50}$ obtained from each study based on the comparison table between microalgae species and cadmium metal with the aim of comparing the sensitivity of various types of plankton. to the heavy metal cadmium in other diatom genera. The IC$_{50}$ value was the concentration of the toxicant which was significantly able to inhibit the growth of *C. gracilis* by 50% for 96 hours. Calculations are carried out using the linear interpolarization method using a program such as ICPIN.

Table 2. List of Cadmium IC50 towards several Phytoplankton Species.

Species	**Cadmium IC$_{50}$ (mg/L)**	**References**
C. gracilis	1,3	[48]
C. gracilis	1.62	
C. gracilis	0.89	[52]
C. gracilis	1.8	[53]
Porphyridium sp.	0.0939	[54]
Navicula sp.	0.9577	[55]
Nitzschia sp.	0,159	[56]
Skeletonema costatum	0,224	
Planothidium lanceolatum	0,25	[57]
P. subcapitata	0,60	[11]
Tetraselmis sp.	3,18	[58]
Isochrysis sp.	0,49	[59]
Thalassiosira sp.	0,32	[60]
Thalassiosira sp.	0.0575	[54]

4. CONCLUSION

Cadmium species in world waterways is reported to be ubiquitously founded. Phytoplankton hold a critical key in maintaining toxic effect of cadmium to ecosystem, since they are playing an important role as primary producer and the base of the food chain in aquatic ecosystem. The various impact of cadmium exposure to phytoplankton is reported to be deteriorated even led to cell mortality.

Various species of microalgae have been studied to have a high level of sensitivity to metal cadmium. Single species were reported to increase its resistency towards cadmium, indicating that the study of toxicological in more diverse species are needed. Furthermore, it is important to study the impact of cadmium to phytoplankton in a cellular level to better understand what mechanism lies and to what extent that the cadmium will be transferred to higher tropical organism via bioaccumulation or biomagnification [61-63].

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