Cylindrospermopsins (cyanobacterial toxins)[1]

Cylindrospermopsin (CYN) and its four variants are naturally occurring alkaloids produced by strains of various species of cyanobacteria, primarily in freshwater environments. They have been found in cyanobacteria around the globe and have most frequently been reported from the cyanobacterial genera *Raphidiopsis* (formerly *Cylindrospermopsis*), *Aphanizomenon* and *Chrysosporum* (see also section 11.5). Unlike MCs, a major fraction of CYNs is often found dissolved in water; particularly at lower temperatures, these toxins may persist even after the producing cyanobacteria are no longer present.

Drinking-water is the most likely route of exposure to CYNs where surface water with cyanobacterial blooms is the drinking-water source. Recreational activities in lakes with cyanobacterial blooms may also be a relevant exposure pathway, potentially to high, usually intermittent concentrations (see WHO *Guidelines on recreational water quality*, 2021). Limited data suggest that CYNs may also accumulate in some food items.

Provisional guideline value (lifetime)	*Total CYNs (sum of all congeners, free plus cell-bound)*: 0.0007 mg/l (0.7 µg/l)
	The guideline value is provisional because of the high level of uncertainty—it is based on data for only CYN and the database is limited, as reflected in the composite uncertainty factor of 1000
Provisional short-term guideline value	*Total CYNs (sum of all congeners, free plus cell-bound):* 0.003 mg/l (3 µg/l)
Occurrence	Concentrations reported usually range well below 1 mg/l; outside of scum areas, they rarely exceed several µg/l. Major fractions (up to 90%) can occur dissolved in water
TDI	0.03 µg/kg bw, based on a NOAEL of 30 µg/kg bw per day for renal pathology observed in an 11-week study in mice and applying an uncertainty factor of 1000 (10 each for inter- and intra-species variability and 10 for database deficiencies,* taking into consideration limitations in the database—in particular, limited data on chronic toxicity, reproductive toxicity and carcinogenicity)
Limit of detection	0.065 µg/L by LC-MS/MS or LC (including HPLC) followed by UV/PDA detection. LC-MS/MS has the highest specificity and sensitivity but requires quantitative reference standards for each CYN in the sample. For UV/PDA detection, the signal from one can be used to estimate the concentrations of each.
	Prior extraction of cells with freeze–thaw cycles and water or methanol/water is necessary for cell-bound CYNs; neglecting extraction from cells will lead to dramatic underestimation of concentrations.
	0.05 µg/l by commercially available immunoassay kits (ELISA); although these are less precise than LC with the above-mentioned detection methods, they capture all CYNs and thus are useful for most monitoring purposes.

[1] As cyanobacteria and their toxins are a concern in many areas and considering the complexities in their management, this chemical fact sheet has been expanded.

Monitoring	The likelihood of blooms can be assessed by understanding water body conditions (in particular, nutrient concentrations, water body depth, water retention time, patterns of mixing and stratification; see section 11.5). Where conditions render blooms likely, visual monitoring of source water (including microscopy for potentially CYN-containing genera) for evidence of increasing cyanobacterial biomass (blooms) is important because biomass can increase rapidly. Exceeding alert values for biomass indicators or CYN concentrations should trigger responses to prevent exposure to elevated toxin concentrations (see the alert level framework in section 11.5). As a major fraction of CYN may occur dissolved in water and be persistent, if blooms of potentially CYN-producing genera have been observed, monitoring should also include toxin analysis for CYNs, if possible. Analysis of cyanotoxins is particularly useful for validating and optimizing the efficacy of control measures such as riverbank filtration or treatment.
Prevention and treatment	Actions to decrease the probability of bloom occurrence include catchment and source water management, such as reducing nutrient loading or changing reservoir stratification and mixing. Filtration is effective for removing intact cyanobacterial cells. For the often large dissolved fraction of CYNs, oxidation with chlorine or ozone at sufficient concentrations and contact times, as well as GAC and some PAC applications, are effective (see chapters 7–10 of *Toxic cyanobacteria in water*; Annex 1).
Guideline value derivation	
• allocation to water	80% of TDI; for short-term exposure, 100% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Additional comments	Total CYNs as gravimetric or molar equivalents should be evaluated against the guideline values since CYNs usually occur as mixtures. Although the guideline values are based on CYN, limited evidence suggests that other CYN congeners have similar toxicity to CYN.
	The provisional short-term drinking-water guideline value is intended to indicate the extent to which the lifetime value can be exceeded for periods of up to about 2 weeks until water treatment can be augmented to bring the concentration of CYNs back under control. It is not intended to allow repeated seasonal exceedances of the lifetime value.
	It is recommended, as a precautionary measure, that bottle-fed infants and small children be provided with an alternative safe drinking-water source (e.g. bottled water that is certified by the responsible authorities) if concentrations are greater than 0.7 µg/L, even for short periods.
Assessment date	2020
Principal references	WHO (2020) *Cyanobacterial toxins: cylindrospermopsins* Chorus & Welker (2021) *Toxic cyanobacteria in water*

* For the short-term guideline value, a database uncertainty factor was applied due to the limited database, including lack of data on reproductive effects after oral exposure, and evidence of potential in vivo genotoxicity of CYNs. An uncertainty factor of 3 was applied because lack of chronic toxicity data does not affect derivation of a guideline value for short-term exposures.

CYN is a potent inhibitor of protein synthesis, and also has cytochrome P450-dependent effects on other processes—for example, DNA damage and induction of cellular stress responses. CYN was the likely cause of a mass human poisoning incident in Australia in 1979.

The provisional guideline values for CYNs are based on a study in male mice using CYN, corroborated by two other studies in both sexes of different strains of mice. The studies demonstrated that a range of organs were adversely affected. The kidneys were identified as the most sensitive organs in these studies, and one study found gender-based differences in the sensitivity of the liver and kidneys. Other studies in mice have demonstrated CYN-induced DNA damage in various organs.

Practical considerations

Where nutrient (phosphorus and nitrogen) concentrations are elevated in lakes, reservoirs or slowly flowing rivers, cyanobacteria occur widely. Where their excessive growth leads to high biomass, sometimes termed "bloom" events, CYNs can reach concentrations in raw water that are potentially hazardous to human health. Such blooms tend to recur in the same water bodies and to be seasonal, whereas others occur perennially. Although some CYN-producing cyanobacteria form scums or accumulate at the thermocline of thermally stratified reservoirs, they tend to not be as pronounced as the scums and accumulations of MC-producing cyanobacteria.

Cyanobacteria are most effectively controlled in the context of developing a WSP (see chapter 4). Control measures to manage potential risks from cyanobacteria, and in particular from their toxins, in drinking-water should include not only adequate treatment, but also measures to control cyanobacterial bloom development. See section 11.5 for more information on cyanobacteria, including further details on monitoring cyanobacterial blooms, the alert level framework, and prevention and management of cyanobacteria in source waters. Effectively minimizing the formation of blooms and locating the raw water intake away from blooms reduce the treatment steps required to remove cyanotoxins.

Drinking-water treatment that removes particles—that is, soil, slow sand or riverbank filtration, conventional water treatment (coagulation, flocculation and filtration or dissolved air flotation) or dissolved air flotation—can remove cell-bound CYNs effectively. Soil, slow sand and riverbank filtration can also remove dissolved cyanotoxins. For all these processes it is important that they are optimized to target the removal of cells and dissolved toxins. While for both pre-oxidation and conventional treatment, cell rupture and toxin release should be avoided, treatment also needs to target the typically large fraction of dissolved CYN. Chlorination and ozonation at sufficiently high doses and contact times are effective for degrading dissolved CYNs; however, elevated organic carbon in bloom situations will substantially increase the disinfectant demand. Chlorine dioxide and chloramine are ineffective for degrading CYNs. GAC and PAC can be effective for removing dissolved CYNs, with efficacy dependent on several factors, including the type of activated carbon, contact times (PAC), flow rates (GAC) and water quality. As the challenges that blooms present for treatment are complex, periodic validation of efficacy during bloom situations and under the specific local conditions is particularly important. Avoiding bloom occurrence and intake is therefore the preferred option.