

Review

# Effects of Microcystins, Cyanobacterial Toxins, on Mammalian Cells and Organs

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*Dedicated to the memory of Professor Franc Gubenšek*

## Abstract

Microcystins are hepatotoxic cyclic heptapeptides characterized by the presence of non proteinogenic  $\beta$ -amino acid ADDA. They are produced by numerous bloom forming cyanobacterial genera. Acute lethal intoxications of humans are rare, but especially chronic exposure to these toxins presents a serious threat to the health of human population. Microcystins enter cells mostly via bile acid transporters; therefore liver is the main target organ in acute intoxication. It has been shown that microcystins are potent inhibitors of intracellular protein phosphatases 1 and 2A. This leads to hyper-phosphorylation of a number of intracellular structural and signal proteins, activation of caspases, and apoptosis of the affected cells. Tumour promoting effects of microcystins have also been described. Considering reports by several authors showing harmful effects of long term exposure to microcystins in several highly populated regions of the planet it must be emphasized that high safety measures should be taken in monitoring the quality of water and food used in human nutrition and medical care.

**Keywords:** Microcystin, cyanobacteria, lungs, brain, heart, kidney

## 1. Introduction

### 1.1. Cyanobacteria

Cyanobacteria are one of the oldest organisms populating the Earth indicating that they have evolved excellent adaptation mechanisms to global climate changes.<sup>1,2</sup> On the other hand, they are also responsible for the near-



**Figure 1:** Formation of the surface *Microcystis aeruginosa* bloom early in the morning. Photograph by B. Sedmak.

extinction of anaerobic life on Earth billions of years ago, but oxygen they released into the atmosphere enabled evolution of other species presently living on the surface of the planet. Killing anaerobic life by liberation of oxygen in the atmosphere was a “collateral damage”, apparently giving no advantage to cyanobacteria. Presently, cyanobacterial toxins present a serious hazard to human health, although killing animals or man has no advantage to the survival of cyanobacteria. Most probably these substances serve a role in the cyanobacterial bloom growth (Figure 1) and competition with other organisms in surface waters; toxicity to mammals being just a side effect.

### 1.2. Cyclic Cyanopeptides

Cyclic cyanopeptides comprise a large and heterogeneous group of biologically active substances that often contain unusual amino acids in their structure. The pathophysiological role of most of these substances still remains to be uncovered, but it is already known that most of these cyclic cyanopeptides either inhibit serine peptida-

ses (“non-toxic” cyanopeptides) or protein phosphatases (microcystins as representatives of hepatotoxic cyanopeptides).<sup>3–5</sup> Not all strains produce hepatotoxic heptapeptides, and the interplay of the effects of cyclic hepatotoxic and non-hepatotoxic cyanopeptides seems to be important for the regulation of cyanobacterial bloom growth and decay.<sup>1,6,7</sup> It has been shown that the “non-toxic” or more precisely non-hepatotoxic anabaenopeptins B and F as well as planktopeptin BL1125, a cyclic cyanobacterial depsipeptide, induce lysis of cyanobacteria by interfering with their metabolism.<sup>8,9</sup>

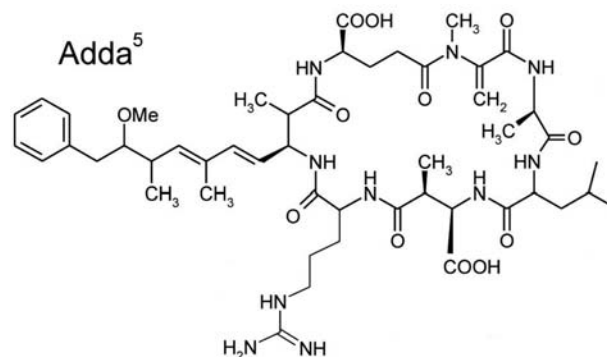
Cyanobacteria are ubiquitous organisms found in freshwater and also in marine environment. They are cosmopolites, and many common species of freshwater cyanobacteria produce different groups of toxic peptides. Cyanobacteria that produce microcystins, hepatotoxic cyclic heptapeptides, can be found in all freshwater bloom forming genera e.g. *Microcystis* (Figure 2), *Anabaena*, *Nostoc* and *Oscillatoria*, *Planktotrix*.



**Figure 2:** Photomicrography of the *Microcystis* surface bloom showing the chroococcal *Microcystis aeruginosa* colonies and the co-occurrence of another filamentous cyanobacterial species in the background.

Under favourable conditions such as water eutrophication these planktonic cyanobacteria readily multiply in marine and freshwater environments forming toxic and/or non-toxic blooms. Toxic blooms can be found in nearly all countries in the world, including Slovenia.<sup>10,11</sup> Drinking contaminated water has caused death of stock and wildlife in many countries.<sup>12–15</sup> This review will focus on the effects of microcystins on mammals. First reports have shown that acute intoxication leads to severe liver damage and extensive intra hepatic haemorrhage, hence the microcystins were considered to be hepatotoxins.<sup>12,16–18</sup> Microcystins comprise a group of almost one hundred cyclic heptapeptides consisting of up to five non proteinogenic and two proteinogenic amino acids in their structure. The most characteristic is the non-protein forming amino acid Adda, which gives the molecule the characteristic absor-

bance at the wavelength of 238 nm. The structure of the most studied microcystin, microcystin-LR is shown in Figure 3.



**Figure 3:** Structure of microcystin LR. Note the presence of the unusual amino acid Adda (source: Wikipedia)

## 2. Microcystin Intoxication

Acute intoxication by microcystins is common in animals, but oral intoxication is less likely to occur in man. Konst et al. have noticed that ingestion of lyophilized *Microcystis aeruginosa* causes congestion of liver with focal necroses in rabbits, mice, guinea pigs, lamb, chickens and duck.<sup>12</sup> Later it has been shown that microcystin LR causes blabbing of rat hepatocytes together with profound disorganization of cytoskeletal microfilaments.<sup>19,20</sup> Hooser et al. have found macro- and microscopic changes in lungs and kidney as well, but they considered those changes as a consequence of the release of detached hepatocytes into the circulation with resulting hepatocellular micro-embolisms of kidney cortex and lungs.<sup>17,21</sup>

Several reports have indicated that chronic exposure to low doses of microcystins poses a serious risk to human health.<sup>22–29</sup> As microcystins have been implicated in tumourigenesis and tumour promoting activity the main concern was the link between cancer and the presence of microcystins in water and food.<sup>14,30,31</sup> Recently it has been shown that other metabolites present in cyanobacteria also possess tumour promoting activity due to their inhibition of gap junctional communication and activation of mitogen-activated protein kinases.<sup>32</sup> Not only liver, but other organs can also be affected during chronic exposure to microcystins, although liver remains the main target due to the rapid uptake of microcystins by hepatocytes. The presence of microcystins in the environment can cause acute intoxications in humans, usually presenting as skin irritation in case of the contact with microcystins in recreational waters, or as mild to severe gastrointestinal problems when swallowing the contaminated water, but a case of pneumonia and even fatal outcome have also been

described.<sup>33,34</sup> Fatal acute intoxications are exceptional – the most extensively reported tragic event occurred in Brazil due to the presence of microcystins in the water used in a haemodialysis unit. Many patients died due to renal and hepatic failure.<sup>35,36</sup> Epidemiological studies have revealed that a long-term ingestion of microcystins in drinking water may be related to liver tumour promotion.<sup>27</sup>

### 3. Biochemistry, Organotropism and Uptake of Microcystins

#### 3.1. Uptake of Microcystins by Mammalian Cells

Most microcystins are polar molecules meaning that free diffusion across cell membranes is virtually impossible. Therefore a transport mechanism must be present in the cells of various organs as microcystins have been detected after oral administration not only in liver but also in lungs, kidneys, enterocytes and brain.<sup>33,37–41</sup> Organotropism can be explained by a selective uptake of microcystins by different cells. The uptake of microcystins occurs primarily by an energy-dependent transport process involving the rifampicin-sensitive hepatic bile acid carrier.<sup>38,42–44</sup> The highest concentration of this type of transporters, belonging to the family of organic anion-transporting polypeptides (OATP/oatp), is found in the liver, which makes it the main target organ. Nevertheless, OATPs are also present in other organs such as heart, kidney, lung and brain.<sup>45</sup> It has also been shown that cyanobacterial bloom extract used in experimental subacute intoxication had a strong suppression effect on the immune function in animals suggesting the presence of these carriers in the lymphocytes as well.<sup>46</sup>

#### 3.2. Inhibition of Protein Phosphatases

Once microcystins enter a cell a profound hyperphosphorylation of cellular proteins can be observed. As the level of protein phosphorylation depends on the balance between the activity of protein kinases and protein phosphatases it was reasonable to assume that microcystins either activate different kinases or inhibit protein phosphatases.<sup>3</sup> Honkanen et al. have shown that microcystin LR is a potent and specific inhibitor of serine/threonine protein phosphatase type 1 and even more so type 2A.<sup>47</sup> Hyperphosphorylation of cytokeratins 8 and 18 occurred at a 3-fold higher rate than other cellular proteins, and this effect may be associated with the tumour promoting effects of microcystins.<sup>48</sup> Recently the crucial role of protein phosphatases inhibition by low doses of microcystin LR and RR has been seriously challenged.<sup>49,50</sup>

#### 3.3. Microcystins and Oxidative Stress

Initial reports suggested that protectants against the reactive oxygen species (ROS) have no effect on microcystin toxicity, but later findings have shown that oxidative stress was an important mechanism of microcystin action.<sup>51</sup> Lyophilized cyanobacterial extract caused lipid peroxidation of hepatocyte membranes and increased production of malondialdehyde.<sup>52</sup> Those findings were confirmed by use of purified microcystin LR instead of cyanobacterial lyophilizate, and the observed inflammation of liver was attributed to the microcystin-induced oxidative stress.<sup>53</sup> Formation of reactive oxygen species observed after application of microcystin LR was considered as a mechanism responsible for the cytoskeleton disruption leading to changes in cell morphology and membrane damage.<sup>54</sup> Initial step in ROS damage seems to be the formation of superoxide radical. Superoxide dismutase abolished the disruption of cytoskeleton, and desferoxamine, the iron chelator, could also partially prevent cytoskeletal alterations.<sup>54</sup> This indicates the importance of Fenton reactions and hydroxyl radical in the ROS-induced damage of cytoskeleton. Recent reports show that antioxidants may have a beneficial effect in microcystin intoxication *in vivo*. Rats fed by antioxidants prior to the exposure to microcystin LR had significantly lower lipid peroxidation of cellular membranes and decreased liver pathology compared to rats exposed only to microcystin LR.<sup>55,56</sup>

#### 3.4. Genotoxic Effects of Microcystins

Oxidative stress is also involved in the DNA damage in hepatocytes as well as in non-hepatic cells, and this effect has been partly attributed to the phosphorylation of a nuclear phosphoprotein p53.<sup>57–59</sup> Other reports have shown that microcystins increase the expression of tumour suppressor gene *p53*.<sup>60</sup> The reduced glutathione (GSH) seems to be important for the DNA repair. Exposure of HepG2 cells to low doses of microcystin LR initially resulted in a decreased concentration of intracellular GSH and an increased DNA damage, but within a few hours the synthesis of GSH increased, and DNA damage was reduced.<sup>61</sup> Cytochrome P450 2E1 released from mitochondria was suggested as the source of ROS.<sup>62</sup> Not only hepatocytes and HepG2 cells but also kidney medulla, brain, lung showed a significant increase in DNA damage after exposure of rats to sublethal doses of microcystin YR.<sup>63</sup> No DNA damage was found in spleen and lymphocytes under the same conditions.<sup>61</sup> DNA damage was also found in rat hippocampus after intra-hippocampal injections of raw microcystin extracts.<sup>64</sup> This was accompanied by clear amnesic effect after injection of 1  $\mu$ L of microcystin extract diluted to 10  $\mu$ g/L. Genotoxic effects of microcystin may be involved in tumour promotion and carcinogenesis as well as in apoptosis.<sup>29,58,65</sup>

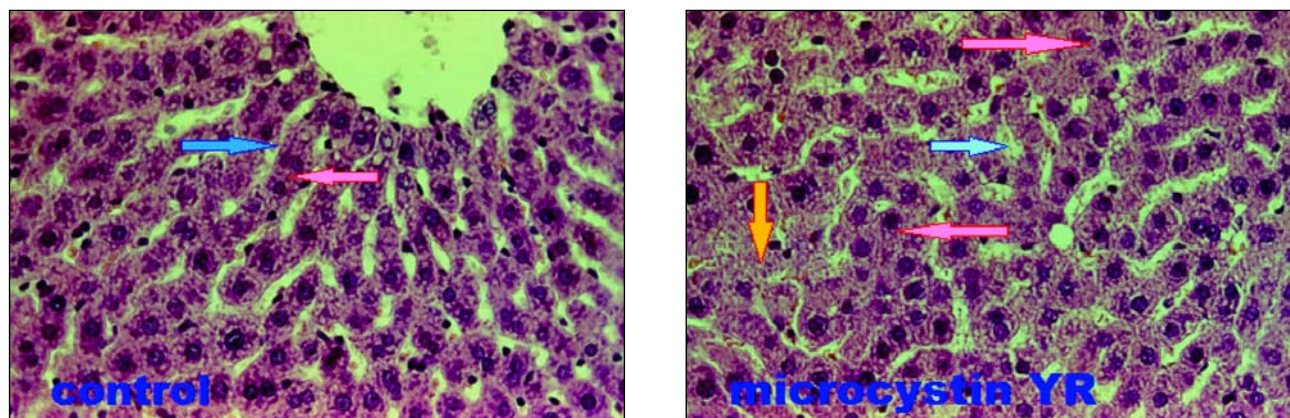
#### 4. Microcystins Alter Cell Morphology and Induce Apoptosis

As described before in detail, majority of the morphological studies of the effects of microcystins was performed on hepatocytes as they are the most susceptible cells to the action of those toxins.<sup>66</sup> Microcystins cause rearrangement of cytoskeletal filaments in rat hepatocytes towards the centre of the cell, cell-to-cell contacts are disrupted, and cells start to bleb. Ultrastructure of liver is disrupted with characteristic dilatation of sinusoids and intra-hepatic haemorrhage. This leads to hypovolemic shock and acute liver failure causing death of experimental animals.<sup>16</sup> It has been shown that hyperphosphorylation of keratin intermediate microfilaments is mainly responsible for the altered hepatocyte morphology.<sup>67</sup> Another observation in a variety of cells was the microcystin-induced condensation of chromatin indicating DNA damage. Cell morphology was not affected only in hepatocytes but also in other cells. Cell shape is maintained by a precise organisation of microfilaments building a dynamic structure – cytoskeleton. In rat kidney cells and fibroblasts the microcystin-induced inhibition of protein phosphatases 1 and 2A caused hyperphosphorylation of cytoskeletal proteins such as microtubules, intermediate filaments, and microfilaments leading to a progressive collapse of cytoskeleton towards the cell nucleus, but actin polymerization and compaction resulted in a star-like structure radiating from the centre of the cell towards the plasmalemma.<sup>68,69</sup> Actin condensation was followed by redistribution of alpha-actinin and talin.<sup>70</sup> Exposure of rats to microcystin YR (MCYR) injected intraperitoneally for three weeks revealed a decreased expression of cytokeratin K8/K18, an increased staining of laminin and desmin while the staining of vimentin remained at the control level.<sup>66,71</sup> Morphological evidence of DNA damage presents as chromatin condensation.<sup>58</sup> DNA fragmentation has been proven by use of different methods.<sup>57,61,62,72</sup> Overall, the morphology changes are typical of apoptosis, but Alverca suggested that autophagy is an important effect of microcystin LR on renal cell line Vero-E6.<sup>73</sup> Cells exposed to microcystins bleb and disintegrate into fragments of different size and shape.<sup>74–77</sup> Externalization of cell membrane phosphatidylserine, an early stage in the process of apoptosis, is also evident.<sup>78</sup> The mechanism of microcystin-induced apoptosis is still elusive, although mitochondria and oxidative stress may play a pivotal role in the execution of cell death. Several mechanisms have been proposed to explain the initiation of apoptosis by microcystins. Presently it seems that mitochondria are involved in ROS formation and consequently to the death of cells exposed to microcystins. An elevation of mitochondrial  $\text{Ca}^{2+}$  increases mitochondrial permeability, and either a chelator of intracellular  $\text{Ca}^{2+}$  or ruthenium red, an inhibitor of mitochondrial  $\text{Ca}^{2+}$  uniporter and Ryanododine receptors, prevented the increase of mitochondrial per-

meability, release of cytochrome c from mitochondria, and attenuated apoptosis of rat hepatocytes.<sup>79</sup> In cultured rat hepatocytes the release of cytochrome c did not result in a formation of apoptosome and no activation of caspases 3 and 9 was observed, but apoptosis seemed to be initiated by cytosolic calcium that activated the calcium binding protease calpain, but other authors have shown that microcystin-LR induced phosphorylation of  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase CaMKII and phosphorylation of myosin light chain are responsible for the formation of apoptotic blebs and for microcystin-induced apoptosis, but activation of caspases also seems to be important.<sup>80–84</sup> Another important event in microcystin-induced apoptosis is phosphorylation of the nuclear phosphoprotein p53.<sup>59</sup> Although apoptosis is clearly a consequence of microcystin intoxication many reports indicate that microcystins are also tumour promoters stimulating cell survival. It seems that phosphorylation of different proteins and interplay between the pro-apoptotic, mitogenic and cell survival promoting proteins is crucial for the end-effect of microcystins on cells. Liver cell hyperplasia observed in prolonged sublethal exposure of rats and rabbits to microcystin LR may be explained by the effects of microcystins on glycogen synthase kinase  $\beta$ .<sup>71,85</sup> This enzyme normally phosphorylates  $\beta$ -catenin, which leads to its degradation in proteasomes.  $\beta$ -catenin is involved in hyperplasia and tumour progression. Since microcystin LR suppresses glycogen synthase kinase  $\beta$  the levels of  $\beta$ -catenin increase and promote cell survival.<sup>86</sup> On the other hand, microcystins activate mitogen-activated protein kinase, which in turn phosphorylates several proteins including p53.<sup>87</sup> The phosphorylated p53 induces apoptosis by activating downstream events and by induction of proteosomal degradation of  $\beta$ -catenin.<sup>86</sup> Recent reports have shown that not only phosphorylation but also expression of several proteins involved in regulation of cell growth and death is altered after exposure of cells to microcystins LR and RR.<sup>49,84,88</sup> It seems that acute intoxication by microcystins leads to cell damage that cannot be repaired, and p53 promotes apoptosis. However, if the levels of p53 are low then chronic exposure to sublethal and non-cytotoxic doses of microcystins leads to cell proliferation and tumour promotion.<sup>86</sup>

#### 5. Effects of Microcystin on Liver and on Cultured Hepatocytes

Microcystins have caused human intoxications world-wide, therefore it is important to provide accurate safety measures regarding the presence of these substances in human nutrition. Despite the facts that microcystins affect human health, and that inter-species variations are significant, the search in literature shows that very few studies have been done on cells of human



**Figure 4:** Microcystin YR disrupts cyto-architecture of rat liver. On the left panel liver from control rat shows normal architecture with sinusoids (blue arrow) lined with hepatocytes (red arrow) and running towards the central vein. On the right panel the structure of the liver from rat exposed to sublethal dose of microcystin YR is disrupted with disorganisation of sinusoid structure. Blue arrow shows a collapsed sinusoid, yellow arrow a dilated sinusoid filled with eosinophilic material and cellular debris, and red arrows show disorganised clusters of hepatocytes. Magnification 400x.

origin, and only two studies on the effects of microcystins on primary human hepatocytes have been reported.<sup>42,72,75,89–91</sup>

Effects of toxins on liver structure can be assessed only *in vivo* (Figure 4), and realistic estimation of carcinogenic and tumour promoting potential of microcystins has been done within epidemiological studies. When the experiments are done on cell cultures, not only the origin of the cells but also days in culture greatly affect their response to microcystins.

### 5. 1. Effects on Isolated Hepatocytes in Cell Culture

Rat hepatocytes are a widely used model to study effects of cyanobacterial toxins on cells in culture. They can be readily obtained by perfusion of rat liver with collagenase, and they are easy to culture. When using primary hepatocytes from mammals it is essential to take into account that freshly dispersed cells lose some of the properties of the cells in the organ. Bile acid transporters responsible for the intake of microcystins by hepatocytes may become fully functional only when cultured cells start to form a pseudo-liver architecture, which takes roughly two days after the seeding of the cells.

It is well established that microcystin LR causes fulminant apoptosis in liver after acute intoxication. Although the microcystin-induced apoptosis has been studied comprehensively, the mechanism of this process and the role of caspases are not fully understood, yet. Our comparative data on the effects of microcystin LR on rat and human hepatocytes show that human hepatocytes were more susceptible to the effects of microcystin LR than rat hepatocytes. Human hepatocytes were obtained during major liver resection in patients with tumours, and rat hepatocytes from Wistar rats. The hepatocytes were isolated by a two-step collagenase perfu-

sion, cryopreserved in liquid nitrogen and thawed rapidly in a water bath. before each experiment.<sup>92–95</sup> Two days after seeding rat and human hepatocytes were treated with microcystin-LR in 6.25 to 50 nM concentration. This resulted in a rapid blebbing and detachment of cells from the substrate, compaction of actin filaments, and condensation of nucleus regardless the origin of cells, but human hepatocytes were more susceptible to the action of the toxin than rat hepatocytes as all morphological changes appeared twice as fast in human hepatocytes when using the same concentration of microcystin LR.<sup>75</sup> Dose response curve also revealed a higher susceptibility of human hepatocytes to the action of microcystin LR. The number of intact human cells after 6 h exposure to 25 nM MCLR decreased for 30% while nearly all rat hepatocytes remained intact. On the other hand, caspase activation rose nine-fold in rat hepatocytes while it was negligible in human hepatocytes. This finding indicates that apoptosis may follow different steps in rat and in human hepatocytes.

### 5. 2. Effects of Microcystins on Immortalized Cell Lines

Later the high susceptibility of human hepatocytes for microcystin LR has been confirmed by other authors by comparing the effects of microcystins on primary human hepatocytes and HEK293 cells of renal origin that were stably expressing recombinant human bile acid carriers.<sup>42</sup> Immortalized hepatic cell lines of human origin, such as HepG2 and others, are increasingly popular due to the relatively easy handling of the cells and repeatable responses to different stimuli. Contrary to primary human hepatocytes, which may vary among the patients, the HepG2 cells and other immortalized hepatocytes of human origin, usually preserve their physiological and biochemical characteristics. This property

makes them an attractive model, but one must keep in mind that these cells may differ significantly from the primary hepatocytes in a number of aspects, meaning that the data obtained on HepG2 cells and cells of similar origin must be interpreted with caution, and cannot be simply extrapolated to human hepatocytes from healthy liver.

## 6. Extra-hepatic Effects of Microcystins

The effects of microcystins on other organs than liver were studied less intensively because acute intoxication always showed nearly exclusively hepatotoxic effect. Epidemiologic studies showing deleterious effects of prolonged exposure of humans to low doses of microcystins opened questions about the possible effects of microcystins on kidney, heart, lungs, brain, immune system, enterocytes, endocrine and reproductive system.<sup>45,63,76,96,97</sup> In prolonged exposure to low doses of microcystins chronic inflammation with degenerated glomeruli and thickened basement membranes develops. Cells show ballooning degeneration, apoptosis, and necrosis. Shedding of epithelial tubular cells, dilated tubules filled with eosinophilic homogenous material, and progressive kidney failure develop.<sup>76,98,99</sup> Exposure of rats for eight months to low doses of microcystins LR or YR showed atrophy and fibrosis of the heart muscle.<sup>97,100</sup> Cardiomyocytes were enlarged and reduced in number with decreased myofibril volume fraction.<sup>97</sup> It seems that ROS play an important role in cardiotoxic effects of microcystins.<sup>101</sup> Lung inflammation and atelectases were observed after intraperitoneal injection of toxic cyanobacterial extract.<sup>40</sup> A more detailed study using microcystin LR instead of cyanobacterial extract showed a rapid decrease of lung compliance consistent with a restrictive lung disease. Patho-histology showed inflammatory infiltrations of lung parenchyma and interstitial oedema.<sup>102</sup> A specific organic anion-transporting polypeptide OATP1A2 has been found in blood brain barrier capable of transporting microcystins to the brain.<sup>37</sup> In sub-chronic exposure to sublethal doses of microcystins genotoxic effects were found in rat brain.<sup>63</sup> It has also been shown that microcystins can cause impairment in spatial learning and memory retrieval in rat.<sup>64</sup> Another relevant finding was immunomodulatory effect of microcystins on chicken and human lymphocytes resulting in a reduced cytokine production and increased apoptosis and necrosis of lymphocytes, while the effect on neutrophils seems to be their recruitment and activation.<sup>77,103</sup> Chronic low-dose exposure of mice to microcystins resulted in an increased weight of testes but decreased sperm mobility and viability, increased sperm abnormality, and decreased level of serum testosterone possibly as a result of ROS induced Leydig cell damage.<sup>65,104,105</sup> Oxidative stress has also been impli-

cated in the microcystin induced degenerative changes in rabbit testes.<sup>106</sup> Not only cells of the male reproductive system but also embryonal cells may be affected by microcystins in the environment. Cultured rabbit embryonal cells, but not the whole embryos embedded in zona pellucida, are affected by microcystins in the culture medium indicating that zona pellucida is an effective barrier for embryo protection against microcystins.<sup>96,107</sup> A provisional Guideline Level for drinking water has been determined at 1 µg/L of microcystin-LR. Data on chronic effects of microcystins on liver and other organs, including teratogenicity, reproductive toxicity and carcinogenicity calls for a reevaluation of this value.<sup>29</sup>

## 7. Conclusions

In acute lethal intoxications microcystins act as potent hepatotoxins causing rapid intra-hepatic haemorrhage. In chronic exposure to sublethal doses of microcystins degenerative effects on other organs and carcinogenic or tumour promoting effects may prevail. Epidemiology shows that an increased incidence of primary liver tumours is a consequence of chronic exposure to microcystins. Microcystins are useful tools to study cell physiology, but recently there have also been several attempts to investigate a possible therapeutic value of these substances.

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## Povzetek

Mikrocistini so hepatotoksični ciklični heptapeptidi, ki vsebujejo značilno  $\beta$  aminokislino ADDA. Proizvajajo jih različne cianobakterije. Akutne zastrupitve ljudi so redke, predvsem kronična izpostavitve nizkim dozam teh hepatotoksinov pa predstavlja resno grožnjo za zdravje ljudi. Mikrocistini vstopajo v celice prek prenašalcev za žolčne kisline. Teh je največ v membranah hepatocitov, zato so pri akutnih zastrupitvah jetra glavni tarčni organ. Po vstopu v celice mikrocistini inhibirajo proteinski fosfatazi 1 in 2A, zato pride do hiperfosforilacije številnih encimov in intracelularnih strukturnih ter signalnih beljakovin, aktivacije kaspaz in apoptoze. Poročila o kancerogenosti in prizadetosti številnih organov ob kronični izpostavljenosti nizkim dozam mikrocistinov opozarjajo, da je potrebno upoštevati varnostne meje za maksimalno dovoljene koncentracije teh snovi v človeški prehrani in v medicini.