

# MNF Report

## Microcystins in algae products used as food supplements

*Opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG)\* – (shortened version)\*\**

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In the SKLM opinion on algal toxins from 10/11 April 2003, the Commission expressed its concern that algae-based food supplements may be contaminated with significant levels of microcystins. The SKLM pointed out that there is a need for clarification with respect to their toxicology and the exposure situation. The German opinion was adopted on September 28<sup>th</sup> 2005, the English Version was agreed on June 15<sup>th</sup> 2007.

### Preamble

Particularly products from the algae species *Aphanizomenon flos-aquae* (AFA) in the form of powders, pills, capsules or tablets are advertised as food supplements in the internet, in printed media and non-scientific publications. They are claimed to have positive health effects, especially for children with an attention deficit hyperactivity disorder (ADHD). However, there is no scientific evidence to support these claimed benefits. According to the current state of knowledge, AFA algae marketed in Europe originate from Upper Klamath Lake, Oregon, USA.

If AFA algae grow together with other blue-green algae (cyanobacteria), the latter may be present as contaminants in AFA algae products. One blue-green algae species, *Microcystis aeruginosa*, forms microcystins which are cyclic heptapeptides that have been proven to damage the liver of humans and animals. Although only an inadequate number of samples have been investigated so far, the results indicate that from the more than 60 congeners, primarily microcystin-LR (approx. 90%) is present in AFA algae pro-

ducts. The toxicology of microcystin-LR has been investigated in the greatest detail; however, the data base on this congener is still incomplete. There are still almost no data available on the other known congeners. Therefore, the present opinion addresses only microcystin-LR. A detailed description of the available data is given in the Annex ([www.dfg.de/sklm](http://www.dfg.de/sklm)).

### 1 Acute toxicity

Oral doses of microcystin-LR have an acute toxic effect in rats and mice (LD<sub>50</sub> 5–11 mg/kg bw) and it is significantly more toxic if administered parenterally (LD<sub>50</sub> 0.025–0.15 mg/kg bw).

### 2 Subacute and subchronic toxicity

The subacute and subchronic toxicity of oral doses of microcystin-LR in rats, mice and pigs is characterised primarily by hepatotoxicity. In addition, mice also show histopathological changes in the kidneys. An oral 13-week study in mice resulted in a no observed adverse effect level (NOAEL) of 40 µg/kg body weight / day. A dose of 200 µg/kg bw/day led to histopathological changes in the liver.

\* The Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft (DFG) advises authorities and the government on the safety for health of foodstuffs. Further information on the SKLM activity profile, see [1].

Further detailed information on the work of the DFG-Senate Commission on Food Safety can be provided by Professor Dr. Gerhard Eisenbrand, Food Chemistry and Toxicology, University of Kaiserslautern or by the Scientific Office of the SKLM: S. Guth, M. Habermeyer and B. Kochle-Clemens, e-mail: [sklm@rhrk.uni-kl.de](mailto:sklm@rhrk.uni-kl.de) and also by Dr. H. Strelen, DFG-administrative headquarters, e-mail: [sklm@dfg.de](mailto:sklm@dfg.de).

\*\* Original references are omitted throughout. The original version of this opinion can be obtained through the Scientific Office ([sklm@rhrk.uni-kl.de](mailto:sklm@rhrk.uni-kl.de)).

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### 3 Long-term toxicity and carcinogenicity

Sound data on long-term toxicity as well as adequate studies on carcinogenicity are lacking. In several rat studies, oral or i.p. doses of microcystin-LR given after administration of a tumour initiator, led to the promotion of preneoplastic liver cell foci. Similar studies on mice gave conflicting results; however, they are not conclusive as a consequence of serious experimental shortcomings.

### 4 Genotoxicity

In the majority of the bacterial systems tested, microcystin-LR was not mutagenic; however, it did stimulate the DNA repair system in *E. coli*. A potentially mutagenic effect in mammalian cells has not been adequately investigated. *In vitro* tests with mammalian cells showed DNA damage at concentrations at which apoptosis and/or cytotoxicity has been found as well. Further studies reported oxidative DNA damage in rat hepatocytes and human hepatoma cells at concentrations not considered cytotoxic. *In vivo* studies showed that i.p. doses of microcystin-LR induced DNA strand breaks in mice and oxidative DNA damage in the rat liver.

### 5 Mode of action

Microcystin-LR inhibits the serine/threonine protein phosphatases 1 and 2A by covalent binding. The resulting hyperphosphorylation of cellular proteins is regarded as the key mechanism in the hepatotoxicity caused by microcystin-LR.

### 6 Guidance values

On the basis of a NOAEL of 40 µg/kg bw/day (13-week study of mice), a provisionally tolerable daily intake (PTDI) of 0.04 µg/kg bw was derived for microcystin-LR by the WHO (1998) and substantiated in detail (WHO, 1999). The PTDI includes an additional safety factor of 10 to account for the lack of studies on long-term toxicity and the conflicting data on carcinogenicity. The overall safety factor was 1000. Based on this PTDI value, the WHO has recommended a drinking water guidance value for microcystin-LR of 1 µg/l, presuming a daily intake of 2 litres *per* person (60 kg bw). This value also accommodates the assumption that 80% of the microcystin-LR intake is *via* drinking water. According to the available information, this drinking water guidance value is being enforced in Germany, Norway and Switzerland.

On the basis of the PTDI value established by the WHO, a guidance value of 1 µg microcystin-LR/g AFA algae was issued for AFA algae in the USA. This was based on the assumption that algae products are the only dietary source

of microcystins and that the daily intake of AFA algae is 2 g *per* person (60 kg). However, microcystin-LR concentrations of up to 33 µg/g were measured in commercially available AFA algae products. In the USA, a total of 87 samples were screened for microcystin-LR between 1996 and 1999; 70% of the measured values were higher than the guidance value of 1 µg/g. An intake of up to 3 g AFA algae/day, as recommended by the manufacturers, thus may lead to a considerable exceedance of the PTDI of the WHO even without taking into account a possible additional intake *via* drinking water.

Although food supplements from *spirulina* and *chlorella* algae were also found to contain microcystin-LR, they appeared to have lower contamination levels than AFA products. However, these findings require further validation.

### 7 Conclusion

Microcystin-LR is a potent hepatotoxic agent. There is evidence that microcystin-LR may act as a tumour promotor in the rodent liver. There is also evidence that microcystin-LR can initiate DNA damage, both *in vitro* and *in vivo*. However, adequate studies on the long-term toxicity and carcinogenicity of microcystin-LR are lacking. In view of the available contamination data, the intake of AFA algae products as recommended by manufacturers may result in the exceedance of the PTDI for microcystin-LR. Therefore, according to the current level of understanding, a human health risk can not be excluded if such products are consumed regularly.

### 8 Research needs

There is a need for further research with respect to the development of suitable analytical methods for toxicologically relevant microcystins in algae products. The mechanism of the genotoxic effect observed *in vitro* and *in vivo* requires clarification. For an adequate assessment of microcystin-LR in algae products used as food supplements, data on long-term toxicity and carcinogenicity is required. Furthermore, there is a considerable need for research on the toxicology of other toxins from blue-green algae that may contaminate food.

The literature comprises data provided from 1997–2004. For further information, see review by Van Apeldoorn *et al.* [2].

### References

- [1] Eisenbrand, G., The DFG-Senate Commission on Food Safety (SKLM). *Mol. Nutr. Food Res.* 2005, 49, 285–288.
- [2] Van Apeldoorn, M. E., van Egmond, H. P., Speijers, G. J. A., Bakker, G. J. I., Toxins of cyanobacteria. *Mol. Nutr. Food Res.* 2007, 51, 7–60.