

## 6. Evaluation and Rationale

There is *inadequate evidence* in humans for the carcinogenicity of microcystin-LR.

There is *inadequate evidence* in humans for the carcinogenicity of nodularin.

There is *inadequate evidence* in experimental animals for the carcinogenicity of microcystin-LR.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *Microcystis* extracts.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nodularins.

### Overall evaluation

Microcystin-LR is *possibly carcinogenic to humans (Group 2B)*.

In three experiments in rats, Microcystin-LR promoted preneoplastic lesions of the liver. In a study in mice, microcystins promoted preneoplastic foci in the colon and a limited subchronic study with microcystin-LR resulted in persistent neoplastic nodules in mouse liver.

Strong evidence supports a plausible tumour promoter mechanism for these liver toxins. This mechanism is mediated by the inhibition of protein phosphatases 1 and 2A, an effect observed in rodents as well as in primary hepatocytes *in vitro*. The resulting hyperphosphorylation of intracellular protein leads to disruption of intermediate filaments that form the cellular scaffold in human and rodent hepatocytes. These toxins modulate the expression of oncogenes, early-response genes and of the cytokine, tumour necrosis factor  $\alpha$ , and affect cell division, cell survival and apoptosis.

*Microcystis* extracts are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Nodularins are *not classifiable as to their carcinogenicity to humans (Group 3)*.