TOXICOLOGICAL SUMMARY AND SUGGESTED ACTION LEVELS TO REDUCE POTENTIAL ADVERSE HEALTH EFFECTS OF SIX CYANOTOXINS

May 2012

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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FINAL REPORT

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Executive Summary

Purpose: Worldwide, several species of cyanobacteria produce cyanotoxins that cause human illnesses and kill pets or livestock. Cyanobacteria bloom in California's surface water bodies. These blooms have caused public alarm but local health officials have lacked a health basis for actions such as posting warning signs. The California State Water Resources Control Board (SWRCB) contracted with the Office of Environmental Health Hazard Assessment (OEHHA) to provide risk assessment support on cyanobacterial toxins. OEHHA conducted a risk assessment to determine the cyanotoxin concentrations at which no adverse effects are expected to occur. The risk assessment includes two parts: toxicity assessment and exposure assessment.

Toxicity assessments are conducted on specific chemicals. A toxicity assessment has two parts – identifying the type of hazard and evaluating the dose response. There is sufficient toxicological information to develop reference levels that reflect the degree of toxicity for six cyanotoxins: anatoxin-a, cylindrospermopsin and the four microcystins; LA, LR, RR, and YR. Hazards posed by these cyanotoxins include liver damage, kidney damage and neurotoxicity. OEHHA computed a dose above which adverse health effects could occur. This is called a Reference Dose (RfD). The RfDs are based on the published literature for each chemical based on the serious health effect occurring at the lowest dose. RfDs differ for acute one-time and subchronic multi-day exposures. OEHHA computed separate RfDs for humans, pets, and livestock.

Exposure assessments quantify the dose of chemicals people or animals take in assuming different scenarios. People can inadvertently ingest contaminated water during recreational uses of surface water such as swimming, boating, and waterskiing. In addition, these recreational users can inhale toxins that are aerosolized, and can absorb toxins through their skin. People fishing in a contaminated area may later be exposed to cyanotoxins when they ingest the contaminated fish or shellfish they caught. Equations relate cyanotoxin concentrations in water or fish to doses people ingest, inhale and absorb through the skin for each of these scenarios. Pets can ingest cyanobacterial scum or drink contaminated water.

Action Levels: OEHHA computed health-based water concentration levels (also known as "action levels"), for people, pets and livestock. Health based concentrations in sport fish and shellfish were also computed. The human water levels are only applicable to incidental exposure through recreational use. They should not be used to judge the acceptability of drinking water concentrations. The exposure equations and RfDs described above were used to calculate suggested action levels. The following table shows the results of these computations.

Preface

This document was developed under a contract between the State Water Resources Control Board (SWRCB) and the Office of Environmental Health Hazard Assessment (OEHHA). OEHHA and SWRCB are members of the California Environmental Protection Agency (Cal/EPA). SWRCB is charged with protecting California's waters. OEHHA scientists have expertise in toxicological evaluations. OEHHA frequently provides support for human and nonhuman risk assessment issues. SWRCB asked OEHHA to provide toxicological assessments, exposure assessments and action levels for six cyanotoxins that had been prioritized by the USEPA: anatoxin-a, cylindrospermopsin, microcystin LR, microcystin RR, microcystin YR and microcystin LA. Several other cyanotoxins are present in California and require the attention of regulatory and resource agencies. Limited funds and the availability of toxicological information narrowed the scope of this report to these particular cyanotoxins.

The Final Draft of this report was completed in June 2009. The State's budgetary crisis at the time delayed the SWRCB's ability to contract with the University of California to arrange an external peer review of the document in compliance with the California Health & Safety Code section 57004. OEHHA received the peer review comments in June 2011. In the meantime, more literature on cyanotoxins has been published. In general, literature published after 2008 was not integrated into this document. However some pertinent recent findings that were highlighted by the peer reviewers were added to the report.

The four peer reviewers of the document were: Dr. Adam Bownik of the John Paul II Catholic University of Lubin, Poland; Dr. Wayne Carmichael of Wright State University, United States; Dr. James Haney of the University of New Hampshire, United States; and Dr. Brett Neilan of University of New South Wales, Australia. Peer reviewer selection was facilitated through the University of California.

OEHHA appreciates the thorough reviews provided by these individuals. Their comments and insight have prompted us to clarify and improve this document in several areas. The peer review comments and OEHHA's responses are available at: http://www.waterboards.ca.gov/water_issues/programs/peer_review/peer_review_cyanotoxins.shtml

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I. Introduction

Some species of cyanobacteria (also called blue-green algae) produce toxins, collectively referred to as cyanotoxins. Several cyanotoxins are extremely toxic to laboratory animals and have poisoned people. Cyanobacteria and cyanotoxins are found in lakes, reservoirs, rivers and estuaries throughout the world, including California, although the amount can vary drastically between water bodies and times of the year. People swimming, waterskiing, or boating in these water bodies can be exposed to cyanotoxins. Cyanotoxins may also accumulate in fish that are caught and eaten by people. Finally, pets and livestock have died after drinking water contaminated with cyanotoxins. California public health officials need a basis for decisions regarding recreational and other uses of these water bodies. This report provides a basis for these decisions:

- The report summarizes published toxicological information concerning six cyanotoxins: anatoxin-a, cylindrospermopsin, microcystin LR, microcystin RR, microcystin YR and microcystin LA
- Using this published information, the report establishes reference doses for each of these toxins above which adverse health effects could occur.
- The report describes methods for estimating exposure during recreational use of water bodies and combines these exposure estimates with the reference dose to estimate water and sportfish concentrations for each toxin that protects recreators.
- Similarly, the report describes methods for estimating exposure to domestic animals and combines these exposure estimates with the acute and subchronic reference doses to estimate water and crust concentrations for each toxin to protect pets and livestock.
- The report provides a literature survey of the effects of cyanotoxins on aquatic ecosystems.

More specifically, in this research effort the Office of Environmental Health Hazard Assessment (OEHHA) staff have:

1. Identified the health effects (in both humans and domestic animals) that may occur upon exposure to the six cyanotoxins.
2. Determined dose levels that may result in adverse health effects for various exposure durations.
3. Identified routes by which exposure may occur under various exposure scenarios.
4. Developed scientifically based health protective “action levels” that may be applied as needed, by local, regional, state or tribal entities throughout California, to reduce (or eliminate) algal toxin exposures.
5. Highlighted any data gaps or areas of further research that may be useful in addressing the challenges identified with this work.

exposure was estimated to be approximately 1.2 kg/day by utilizing some basic observations in livestock, the details of which are in Appendix V. Calculated threshold concentrations in dried crusts or mats for the intake rate of 1.2 kg/day in dairy and beef cattle are presented in Tables 7 and 8. Action levels for cyanobacterial crusts and mats should be reported in dry weight since these materials are typically dry or moist. Cyanobacterial crusts and mats may be hazardous whether they are floating or landed.

Small breed dairy cows were used for the dairy cow exposure estimates because they have the potential for the greatest exposure. The intake of 1.2 kg of cyanobacterial crusts and mats was divided by the average weight for small breed dairy cattle (454 kg) to estimate an intake rate of 0.0026 kg crusts or mats per kg body weight per day (kg/kg-d; see appendix V for details). We applied the uncertainty factor of 3 to the estimated intake rate of 0.0026 kg/kg-d which resulted in a final exposure level of 0.008 kg material/kg-d. The RfDs (mg/kg-d) for the cyanotoxins were divided by the final crusts and mats consumption level of 0.008 kg material/kg-d resulting in a chemical concentration in cyanobacterial crusts and mats (mg/kg) that would result in exposure at the RfD level or below. This concentration was set as the action level. Action levels are presented for both acute (<24h) and subchronic (up to 10% of lifetime) durations of exposure. Cyanotoxin action levels in cyanobacterial crusts and mats for dairy cows are shown in Table 7.

For microcystin, the acute RfD for domesticated animals (0.037 mg/kg-d) was divided by the final exposure level of 0.008 kg/kg-d (the product of dairy cow crusts and mats consumption, 0.0026 kg crusts or mats/kg-d, and an uncertainty factor of 3) to calculate 4.6 mg microcystin/kg crusts or mats, which was rounded to 5 mg/kg to become the acute microcystin action level in cyanobacterial crusts and mats for dairy cows (Table 7). The subchronic microcystin RfD for domesticated animals (0.00064 mg/kg-d) was divided by the final exposure level of 0.008 kg/kg-d (the product of dairy cow crusts and mats consumption, 0.0026 kg crusts or mats/kg-d, and an uncertainty factor of 3) to calculate 0.08 mg microcystin/kg crusts or mats, which was rounded to 0.1 mg/kg to become the subchronic microcystin action level in cyanobacterial crusts and mats for dairy cows (Table 7).

For anatoxin-a, the acute RfD for domesticated animals (0.025 mg/kg-d) was divided by the final exposure level of 0.008 kg/kg-d (the product of dairy cow crusts and mats consumption, 0.0026 kg crusts or mats/kg-d, and an uncertainty factor of 3) to calculate 3.1 mg anatoxin-a/kg crusts or mats, which was rounded to 3 mg/kg to become the acute anatoxin-a action level in cyanobacterial crusts and mats for dairy cows (Table 7). The same RfD, and thus action level, was determined to most appropriately represent subchronic exposures to anatoxin-a (see the discussion for the computation of anatoxin-a RfDs for domesticated animals under the subsection *Health-Based Criteria for Anatoxin-a*).

For cylindrospermopsin, the acute RfD for domesticated animals (0.04 mg/kg-d) was divided by the final exposure level of 0.008 kg/kg-d (the product of dairy cow crusts and

Appendix I: Determination of Swimmer Exposure

This scenario is designed to ensure that people swimming are not exposed to concentrations of cyanotoxins that could cause adverse health effects. Cyanotoxins in the water could theoretically enter the swimmers bloodstream by three routes.

1. Ingestion: Swimmers, especially children, accidentally swallow the water in which they are swimming.
2. Dermal uptake: Some chemicals are absorbed through the skin of swimmers.
3. Inhalation: Volatile chemicals or those in aerosols may be present in the air above the water. The swimmer may inhale these vapors or aerosols while swimming.

Dose from Water Ingestion

Swimmers may inadvertently swallow (ingest) water while swimming. Cyanotoxins in the swallowed water can be absorbed into the blood from the stomach and intestines. The amount of a toxin ingested is proportional to the amount of water that is swallowed, the concentration of chemical in the water, the absorbed fraction, and the time spent swimming, and inversely proportional to the body weight. The absorbed dose is calculated using the following equation:

$$D_{ingest} = \frac{C_w \times ET \times IR \times Abs}{BW} \qquad \text{eq. A.I-1}$$

where:

D_{ingest} = Dose from ingesting water while swimming (mg/kg/event),
ET = Exposure time (hrs/event),
IR = Ingestion rate (L/hr),
C_w = Chemical concentration in water (mg/L),
Abs = Fraction absorbed (assumed to be 100 percent),
BW = Body weight of exposed individual (kg).

The variables for this and the following equations are shown in the tables below.

Dose from Skin Penetration

Some chemicals can penetrate the skin to reach the blood. The following equation shown below is how the absorbed dose is calculated for those chemicals:

$$D_{dermal} = \frac{C_w \times ET \times SA \times K_p \times R_1 \times R_2}{BW} \qquad \text{eq. A.I-2}$$

where:

D_{dermal} = Dose from dermal penetration while swimming (mg/kg-event)

ET = Exposure time (hrs/event),
SA = Surface area of exposed skin (m^2),
C_w = Concentration in water (mg/L),
K_p = Chemical-specific dermal permeability coefficient (cm/hour),
BW = Body weight of exposed individual (kg).
R_1 = Conversion factor for square meters to square centimeters (10,000 cm^2/m^2)
R_2 = Conversion factor for cubic centimeter to liters (0.001 L/cm^3)

As in all the other equations, the intake dose is proportional to the time swimming (ET), the concentration of chemical in the water (C_w), the surface area of the person (SA), and inversely proportional to the body weight. The absorbed dose is proportional to the dermal permeability coefficient (K_p), a physiochemical property of the chemical indicating its ability to penetrate skin.

Dose from Inhaled Vapors

Volatile chemicals may vaporize from the water into the air above the water. A swimmer would inhale these chemicals while swimming. The following equation shows how the intake dose was calculated.

$$D_{inhaled} = \frac{C_a \times ET \times IR}{BW} \qquad \text{eq. A.I-3}$$

where:

$D_{inhaled}$ = Dose from inhaling vapors in air while swimming (mg/kg-event)
C_a = Ambient vapor or aerosol concentration in air (mg/m^3),
ET = Exposure time (hours/event),
IR = Inhalation rate (m^3/hour),
BW = Body weight of exposed individual (kg)

$$C_a = C_w \times H' \times R_3 \qquad \text{eq. A.I-4}$$

where:

C_w = Concentration in water (mg/L), and
H' = Chemical specific Henry's Law Constant ($\mu g/m^3$ air per mg/L water)
R_3 = Conversion factor for micrograms to milligrams (0.001 mg/µg)

The intake dose is proportional to the time spent swimming (ET), the inhalation rate (IR) and the concentration in air (C_a). Air concentrations are predicted using the Henry's Law constant that is a property of the chemical.

Lesser flamingos that died during a mass mortality event had been feeding on blooms of *Arthrospira fusiformis* and contained anatoxin-a concentrations up to 5.82 µg/g ww in liver [268]. The potential for anatoxin-a to move through the food web is unknown. The chemical properties of this toxin could result in negligible transfer from prey to predator. However, more studies are needed to validate this presumption.

Conclusions and Research Needs

In conclusion, aquatic organisms residing in water bodies with recurrent cyanobacterial blooms are likely exposed to sublethal levels of cyanotoxins. The species that are exposed will depend on the toxin's movement through the food web. The sublethal toxicity of microcystins is well described. However, more work is needed on the potential impacts from maternal transport of this toxin to developing organisms. More research is needed to understand the sublethal impacts of cylindrospermopsin and, especially, anatoxin-a on aquatic organisms. The existing literature on microcystins, and perhaps cylindrospermopsin, could be used to determine sublethal toxicity thresholds in dietary items and predator tissues. This would facilitate the protection of aquatic organisms by wildlife managers and regulators. There is a strong need for an understanding of cyanotoxin effects on aquatic mammals. Additionally, transfer of cyanotoxins to terrestrial animals deserves more attention. Several recent reviews have focused on research needs for a better understanding of the impacts of cyanotoxins on humans and animals [312-316]. Most of these reviews emphasize the need to investigate the toxicological properties of mixtures of cyanotoxins since they are most relevant to field exposures.

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